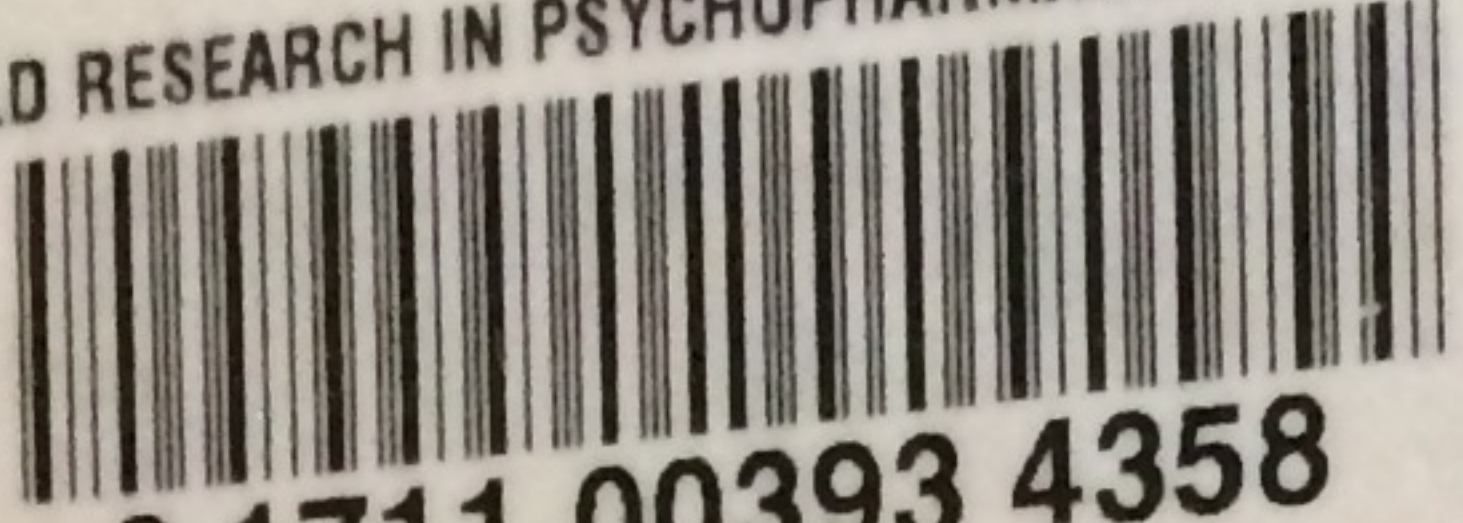


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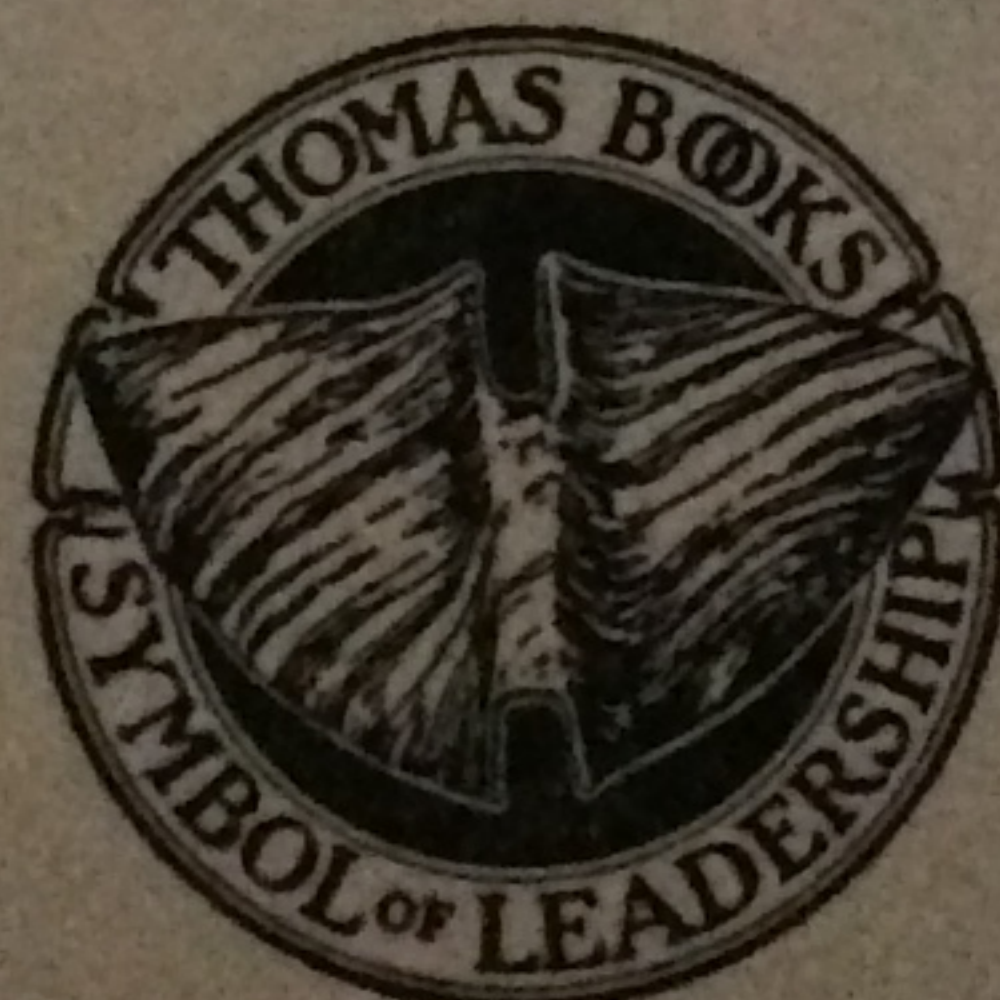
Child Research
In Psychopharmacology

Child Research In Psychopharmacology

Organized and Edited by
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With a Foreword by
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Child Research in Psychopharmacology

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FOREWORD

FOR SEVERAL years the National Institute of Mental Health has supported an extensive program of research in psychopharmacology. This research has proceeded along many different lines, such as synthesis of new drugs, exploration of the biological and psychological mechanisms of drug action, development of new screening techniques, and clinical evaluations of drugs for mentally ill patients.

While much of this research has relevance, of course, for the use of drugs with children, the Institute felt that a conference pointed directly at the problems of child research in psychopharmacology was necessary and important. The obstacles involved in obtaining valid knowledge about drug effects in adults are compounded when we turn to children. The child is clearly not a miniature adult, and must be studied in his own right. The question of side effects—favorable and unfavorable, immediate and delayed—is particularly crucial with children, since psychological and physiological development can be affected at so many different stages and in so many different areas. We must recognize that these drugs when used with children may not only be tools of tremendous value but also may contain elements of danger.

We must learn—slowly, perhaps—wherein these values and possible dangers lie. My emphasis here is on what we need to learn, rather than what we already know, about the psychopharmacological agents. This same research emphasis pervaded the conference. The participants, in the very course of confessing their ignorance, were in many respects the architects of a plan for obtaining sound knowledge about the use of drugs with children. This plan, containing directions and suggestions for the best methods of doing research in this field as well as delineation of some of the many pitfalls to be avoided, will be of great value to those of us who must be concerned with a national program of research in mental health. We are grateful to all the participants and observers at the conference for coming to Washington to

talk about these urgent problems. Now that the conference is over, we hope that they were all encouraged by it to return to their clinics, hospitals, and laboratories to continue their attack on these problems with even greater vigor. We also hope that readers of this volume will be able to contribute their efforts toward this same goal.

R. H. FELIX, M.D., *Director*
National Institute of Mental Health

PREFACE

THE CONTENTS of this volume are based primarily upon the proceedings of a conference on Child Research in Psychopharmacology, sponsored by the Psychopharmacology Service Center of the National Institute of Mental Health. The conference was held at the Hotel Statler in Washington, D. C., on October 27, 1958,* and was chaired by Dr. Milton J. E. Senn. Following brief welcoming remarks by Dr. Joseph M. Bobbitt, Assistant Director of the National Institute of Mental Health, and Dr. Jonathan O. Cole, eight formal papers were presented, each accompanied by one or two discussions. Along with Dr. Senn's closing comments, papers based on these contributions constitute Chapters 2 through 10.

The conference participants represent such diverse disciplines that I would expect that any professional worker or advanced student interested in drugs or children might benefit from the material. However, since this area is still in its infancy (no pun intended!), I thought it might be both appropriate and helpful to the reader to include two special chapters: (a) a brief overview of general psychopharmacology, with emphasis on clinical effects, and (b) an annotated, indexed reference list on the use of psychopharmacological agents with children.

I have long believed that speed of publication is of the essence in communicating conference proceedings. With the fine cooperation of the publisher, this manuscript is expected to appear in print approximately six months after the conference. This left me two months in which to organize and edit the manuscript—an impossible task were it not for the deep understanding of numerous individuals.

To the contributors who so graciously accepted my Simon

* The participants also met in a closed session on October 28 at the National Institutes of Health, Bethesda, Maryland. At this meeting the group discussed, relative to the future plans of the Psychopharmacology Service Center, some of the major points brought out on the previous day.

Legree veneer in requesting early receipt of papers, I would like to express my gratitude, admiration—and awe. Attempting to meet deadlines seems to be the story of our lives.

Lorraine Bouthilet and Carmen Eldridge of the Psychopharmacology Service Center staff assisted me materially in the editorial process. In handling the conference papers, I tried to give some uniformity and consistency to style of presentation. Many of the informal comments—and unfortunately some of the best jokes—had to be eliminated. In some instances I have added headings and changed sentence structure. At all times I have tried to avoid altering the basic meaning. While I would have preferred to get the contributors' approval of these changes prior to publication, time pressures prevented this safeguard. Hence, final responsibility for all modifications, deletions, and inclusions rests on my shoulders.

My secretary, Dana Fling, somehow tolerated my impatience during this turbulent period and contributed, along with Margaret Lusk, Virgilyn McCann, and Lillian Venteicher, to the typing of the final manuscript.

Finally, a word of appreciation to Mr. Payne Thomas for arranging such early publication. Charles C Thomas has also kindly agreed that in lieu of royalty payments (which are being waived by the contributors), the retail price of this volume will be appropriately reduced.

SEYMOUR FISHER

INTRODUCTORY NOTE

SEYMOUR FISHER

IT HAS OFTEN been stated that in research, as in other kinds of problem solving, answers are fairly simple to obtain—provided the questions have been appropriately formulated. The Psychopharmacology Service Center, under its general program of promoting research in psychopharmacology,* sponsored the Conference on Child Research in Psychopharmacology to facilitate the search for relevant and precise questions.

The primary objectives of the conference were as follows:

1. To focus on basic short- and long-term problems of drug effects on psychological functions, family relationships and community adjustment, maturational and developmental processes, and the central nervous system; on the type of child (i.e., disturbed, psychotic, normal, etc.); and on research methodology and measuring instruments;
2. To develop new hypotheses and approaches to the study of drug effects in children, taking into consideration historical background variables and personality differences; situational variables such as stress, motivation, rewards and punishments; and socio-environmental variables such as clinic, school, and family atmospheres;
3. To pave the way for initiating long-term developmental studies;
4. To stimulate further research interest in drug research with children.

Of all these objectives, perhaps the most important one is the last: research stimulation. I am well aware that we do know quite a bit about immediate drug effects in behaviorally disturbed children. I am also acutely aware that there is a great deal more we would like to know—and *need* to know—before

* The Center's chief functions are to stimulate and support basic and clinical research in psychopharmacology, and to offer research advisory and coordinating services to investigators working in this field. Grants in support of research are awarded through the existing grant and award programs of the National Institutes of Health.

these promising agents can be utilized to their best advantage.

In organizing the conference, I was strongly guided by this "need-to-know" orientation. I deliberately attempted to assemble a heterogeneous sample of brain power and to include research workers who have had no actual experience with either drug effects or children. Admittedly, this venture into group dynamics was "experimental" in nature, and some readers may feel that the variability in content did not justify the approach. On the other hand, on the premise that at our present stage of knowledge a broad scope is needed, then it seemed plausible to expect that such an interdisciplinary team might contribute some meaningful new questions.

I believe the participants admirably succeeded in their endeavor. They were asked to emphasize questions rather than answers—questions of philosophical, methodological, and practical importance confronting the clinical and experimental scientist concerned with drug effects in children. Thus, very little research data will be found in the following pages. The reader who is interested in "answers"—confirmed and unconfirmed—accumulated to date, might do well to consult the references listed at the end of this volume.

Much of the recent work on drug effects has dealt with the short-term effect of one or more drugs on clinical symptoms in "disturbed" children. This is certainly important to know. However, it is only one of many equally important questions, some of which may be more difficult to investigate but which are nonetheless compelling. It was perhaps natural that so many of the participants were concerned in one form or another with developmental processes. The possibility of either favorable or unfavorable aftereffects looms large in the minds of many. I am certain that the spirit of wariness, caution, and even apprehension evident in many of the papers was not intended to dampen the enthusiasm of clinicians who are using drugs in their practice. Rather, I suspect that it reflects a serious challenge to the psychopharmacologist to bear down on all aspects of this crucial area. The questions elicited during the conference are by no means metaphysical. Veridical, meaningful answers can, and *must*, be obtained by ingenious and meticulous empirical research—which is sometimes tedious but always gratifying.

CONTENTS

	<i>Page</i>
CONTRIBUTORS	v
FOREWORD	vii
PREFACE	ix
INTRODUCTORY NOTE	xi

Chapter 1

A SYNOPTIC REVIEW OF PSYCHOACTIVE DRUGS *by* Jonathan O.

Cole and C. Jelleff Carr	3
The Scope of Psychopharmacology	3
Phenothiazine Derivatives	5
Rauwolfia Alkaloids	9
Diphenylmethane Derivatives and Substituted Diols	10
Nonbarbiturate Sedatives and Calmatives	14
Antidepressives (Central Nervous System Stimulants)	14
References	19

Chapter 2

BASIC ISSUES IN DRUG RESEARCH WITH CHILDREN: OPPORTUNITIES and LIMITATIONS OF A PEDIATRIC AGE GROUP *by* Leon

Eisenberg	21
Conceptual Problems	21
Special Opportunities Afforded by Studying Children	26
Methodological Problems in Child Psychiatry	31
References	33
Discussion <i>by</i> Laretta Bender	35
References	41
Discussion <i>by</i> Alfred M. Freedman	42
References	46

Chapter 3

BASIC PROBLEMS INVOLVED IN THE USE OF THE NEWER NEURO- PHARMACOLOGICAL DRUGS IN CHILDHOOD *by* Reginald S.

Lourie	48
Use of Drugs in a Children's Hospital	50
Major Research Needs	52
Reference	55

	Page
Discussion <i>by</i> Dane G. Prugh	55
References	61

Chapter 4

POPULATIONS, BEHAVIORS, AND SITUATIONS; SOME ECOLOGICAL
CONSIDERATIONS IN CHILD DRUG RESEARCH *by* Lloyd J.

Borstelmann	62
Situational Variables	65
Developmental and Organismic Sampling Problems	67
Measuring Behavioral Change and "Improvement"	69
The Use of Nonpatient Subjects	73
Summary	74
References	75
Discussion <i>by</i> Kathleen Cole	76
Reference	81
Discussion <i>by</i> Fritz Redl	81

Chapter 5

THE COLLABORATIVE STUDY AS A POSSIBLE TECHNIQUE FOR CHILD
RESEARCH IN PSYCHOPHARMACOLOGY *by* Stewart H. Clifford

Possible Correlations Between the NINDB Collaborative Project and an NIMH Program for Child Research in Psychopharmacology	87
References	89
Discussion <i>by</i> Maurice W. Laufer	93
References	93
	95

Chapter 6

TECHNIQUES OF BEHAVIOR STUDY FOR CHILDREN *by* Boyd R.
McCandless

Physical and Motor Development	96
Intellectual Development and Behavior	97
Emotional Development and Behavior	98
Social Development and Behavior	99
Cognitive Development and Behavior	100
Summary	101
References	101
	103
	104

	<i>Page</i>
Discussion <i>by</i> Emma M. Layman	105
References	109

Chapter 7

THE USE OF OPERANT CONDITIONING TECHNIQUES IN CHILDREN

<i>by</i> Eugene R. Long	111
The Operant Technique	111
Operant Procedures With Children	112
Examples of Behavior With Different Reinforcement Con- ditions	116
Summary	124
References	124
Discussion <i>by</i> Seymour Fisher	125
Reference	127
Discussion <i>by</i> Jacob L. Gewirtz	127
References	135

Chapter 8

COMPARATIVE DRUG-BEHAVIOR ANALYSIS <i>by</i> Sherman Ross . . .	137
Comparative Psychology	137
Developmental Research	140
Problems in Studying Children	144
References	147
Discussion <i>by</i> Jonathan O. Cole	148
Reference	151

Chapter 9

SOME NEUROPSYCHOLOGICAL PROBLEMS RELEVANT TO CHEMICAL

INTERVENTION IN THE GROWING ORGANISM <i>by</i> Lila Ghent	152
Intervention in Central Nervous System Functioning . . .	152
Developmental Problems	156
Developmental Approaches to Brain-Behavior Relations . .	159
Summary	162
References	162
Discussion <i>by</i> Joel J. Elkes	163
References	166

Chapter 10	
CLOSING REMARKS <i>by</i> Milton J. E. Senn	168
Chapter 11	
REFERENCE LIST ON THE USE OF PSYCHOPHARMACOLOGICAL AGENTS WITH CHILDREN <i>by</i> Lorraine Bouthilet and Seymour Fisher	170
Reference List	171
Subject Index to Reference List	202
INDEX	207

Child Research
In Psychopharmacology

Child Research
in Psychology

Chapter 1

A SYNOPTIC REVIEW OF PSYCHOACTIVE DRUGS

JONATHAN O. COLE AND C. JELLEFF CARR

SINCE 1953 increasing numbers of drugs of reported usefulness in the treatment of psychiatric conditions have been developed and are now available to the practicing physician for use in the management of a variety of mental illnesses (2, 8). The majority of these compounds have yet to receive any thorough, well controlled study of their usefulness, even in the schizophrenias. Studies of their effectiveness in the treatment of the neuroses are even more limited in both scope and adequacy. Since similar lacunae exist in the available literature on their use in the psychiatric conditions of childhood, the large number of available compounds must present a confusing picture to pediatricians, psychiatrists, psychologists, and psychiatric social workers who work with emotionally disturbed children. This brief review article is designed to introduce the reader to a few of the pharmacological properties and reported therapeutic actions of these agents.

The Scope of Psychopharmacology

Psychopharmacology represents an area of pharmacology dealing with those chemical substances that selectively affect behavior in animals and man. Psychopharmacology is not a new field in one sense. It was the discovery of compounds producing behavioral effects that might be applied to the pharmacotherapy of mental illness that focused our attention upon the clinical usefulness of these agents in disease states. One might exclude from the classification of psychopharmacological agents the anesthetics, narcotics, and hypnotics, as drugs that are of only incidental value in mental illness. On the other hand, numerous agents of pharmacological interest are known that produce bizarre behavior patterns in animals and man. These compounds, termed halluci-

nogens or psychotomimetics, have yet to find a place in therapy. Psychopharmacology is an area involving fundamentally four major disciplines: the organic chemist for synthesis of chemical compounds; the psychologist for assessment of behavior characteristics; the pharmacologist for studies involving the mechanism of action, patterns of excretion and metabolism, and toxicity; and the psychiatrist and clinical psychologist for eventual clinical evaluation (1, 5).

The main drug groups to be considered are: the *major tranquilizers*, those with apparent or confirmed efficacy in the treatment of hyperactivity and disturbed behavior in psychotic patients; the *minor tranquilizers*, those with reported but generally unconfirmed efficacy in the treatment of neurotic and psychosomatic reactions; the *nonbarbiturate sedatives and calmatives*; and the *antidepressive agents*, most of which are also central nervous system stimulants.

Considered by major chemical groups, one finds in the class of *major tranquilizers* the *phenothiazine derivatives* and the *rauwolfia alkaloids* (Table I). Under the *minor tranquilizers* are found the *diphenylmethane derivatives* and the *substituted diols* (Table II). The *nonbarbiturate calmatives and sedatives* are a chemically heterogeneous group (Table III). One could probably extend with justification this last list to include older drugs such as the bromides, chloral hydrate, and even ethyl alcohol, since it has not been demonstrated that any of these compounds differ significantly from older sedatives and hypnotics (1, 2, 7). The *antidepressive agents* are listed in Table IV. This last group illustrates the great problem in developing a system of classification based on chemical structure. Pipradrol is a diphenylmethane derivative and an isomer of azacyclonol, and orphenadrine is related to diphenhydramine (Benadryl), a compound which has been shown to have a tranquilizing action in disturbed children and which has sedative side effects when used as an antihistaminic in adults. Further, amphetamine, a classical central nervous system stimulant appears to calm children with hyperkinetic behavior disorders. One of the phenothiazines, promethazine (Phenergan), is probably primarily a sedative, lacking the clinical effectiveness in the treatment of

disturbed behavior shared by the other phenothiazines; for this reason, it is not included in Table I. A number of the newer phenothiazines, including perphenazine, prochlorperazine, and trifluoperazine have some stimulant effect in some patients. Mepazine, while not apparently a stimulant, has been described as useful to elevate mood in some depressed patients.

Despite these limitations, the classification has the advantage of grouping together drugs apparently similar in pharmacological action and clinical utility. This classification will serve a useful function until research at the basic and clinical levels permits a more rational and specific classification to be developed. It is evident from this discussion that distinctions between tranquilization and sedation, and between central nervous system stimulation and alleviation of affective depression cannot be drawn with clarity and assurance at the present state of our knowledge.

Phenothiazine Derivatives

The phenothiazine derivatives have a basic chemical structure that easily lends itself to modification. Chlorpromazine was the first phenothiazine discovered that was found useful in a psychiatric setting. As usually happens in medicinal chemistry, when one active drug is found, a variety of related compounds are synthesized and tested for effectiveness and toxicity. These drugs differ from each other chemically in the nature of their substituent groups, but they contain the same basic phenothiazine nucleus. They exhibit differences in their clinical actions, in their relative potency, and in the frequency with which certain types of undesirable side effects occur.

Chlorpromazine (Thorazine). As chlorpromazine is a parent substance, its pharmacology is of interest as reflecting generalizations for the entire group of phenothiazine derivatives. Chlorpromazine evokes a multifaceted psychopharmacological response in animals and man. The drug is rapidly absorbed orally, parenterally, and rectally. Chlorpromazine administered to animals produces a tachycardia and a consistent fall in blood pressure. Cardiac output is reduced as the result of decreased peripheral resistance. The depressor effect and diminished cardiac output are presumably related to chlorpromazine's adrenergic blocking

action, which is one of its characteristic effects. Chlorpromazine is a relaxant to the smooth musculature of the intestines. The motility of the gastrointestinal tract is inhibited by chlorpromazine as the result of its autonomic nervous system action. These psychopharmacological effects which can be demonstrated in laboratory animals explain some of the side actions of the compound. The multiplicity of actions of chlorpromazine bespeaks its use

TABLE I
PHENOTHIAZINE DERIVATIVES AND RAUWOLFIA ALKALOIDS

Generic Name	Trade Name
<i>Phenothiazine Derivatives</i>	
chlorpromazine	Thorazine (Smith Kline & French)
mepazine	Pacatal (Warner-Chilcott)
perphenazine	Trilafon (Schering)
prochlorperazine	Compazine (Smith Kline & French)
promazine	Sparine (Wyeth)
thiopropazate	Dartal (Searle)
trifluoperazine	Stelazine (Smith Kline & French)
triflupromazine	Vesprin (Squibb)
<i>Rauwolfia Alkaloids</i>	
deserpidine	Harmonyl (Abbott)
rescinamine	Moderil (Pfizer)
reserpine	many trade names

in many clinical conditions. It is effective in relieving nausea and vomiting. It has been used in acute alcoholism. Its value as an agent to potentiate the action of analgesic drugs appears to have been demonstrated. However, the principal use of the drug is in the management of psychiatric patients.

Promazine (Sparine). Promazine in most of its pharmacological responses resembles the action of chlorpromazine. The presence of the chlorine atom in the molecule of chlorpromazine apparently intensifies the action of the compound; therefore, the pharmacological responses evoked by promazine (which lacks a chlorine molecule), in the main, are less marked. However, this drug is generally administered in smaller doses than chlorpromazine.

Prochlorperazine (Compazine). Prochlorperazine is an analogue of chlorpromazine. In animals the drug has marked antiemetic activity. The drug lowers the blood pressure of anesthetized dogs when administered intravenously; however, its hypotensive effect is about half that of chlorpromazine. Likewise, the adrenergic blocking action of prochlorperazine is approximately half that of chlorpromazine.

Perphenazine (Trilafon). Perphenazine has actions and uses similar to those of chlorpromazine, but is employed in much smaller doses. Its pharmacological actions are qualitatively similar to those of chlorpromazine. In animals this drug seems to elicit a greater degree of behavior depression accompanied by muscle weakness and ataxia than does chlorpromazine. In acute animal experiments, the agent is approximately half as toxic as chlorpromazine.

Mepazine (Pacatal). Mepazine is another phenothiazine derivative producing psychopharmacological effects similar to those elicited by chlorpromazine. The compound is rapidly absorbed and distributed by the blood to the brain, liver, spleen, kidneys, and lungs. Excretion begins in the urine about three hours after a subcutaneous injection. The metabolic products have not been determined; however, there appears to be no evidence of cumulative action. The principal response elicited by this drug is similar to that produced by chlorpromazine, namely, the production of tranquility without a hypnotic state.

Thiopropazate (Dartal). Thiopropazate is said to be about 5 to 10 times as potent as chlorpromazine in experimental animals. This potency relationship is expressed in the dosage of the drug for patients. Considerably smaller doses of thiopropazate are administered than would be used with chlorpromazine. The drug produces marked tranquilizing action in animals, and it has a potent antiemetic effect.

Triflupromazine (Vesprin). In animals and in man, triflupromazine appears to be approximately three times as potent as chlorpromazine in producing tranquilization. The drug produces a moderate degree of hypotension and may cause orthostatic hypotension in some individuals. It produces a slight to moderate

degree of adrenergic blockage. The agent is an antihistaminic drug.

Trifluoperazine (Stelazine). Trifluoperazine has about 18 times the potency of chlorpromazine in antagonizing the emetic effect of intravenously injected apomorphine in dogs. These data support the clinical observations that trifluoperazine is effective in the treatment of nausea and vomiting in man in a dose far below that required for either chlorpromazine or prochlorperazine. Trifluoperazine and chlorpromazine have similar actions on the cardiovascular system. Both drugs appear to be equally hypotensive, and both possess about the same order of adrenolytic potency. Trifluoperazine is considerably more potent than chlorpromazine in blocking conditioned avoidance responses in rats. The clinical and pharmacological aspects of trifluoperazine have recently been reviewed (6).

Clinical uses of the phenothiazines. An imposing array of evidence from a moderate number of controlled clinical trials and a very large number of uncontrolled clinical studies attests to the ability of chlorpromazine to control hyperactive, disturbed behavior in both schizophrenic states and in manic excitements. The drug is apparently effective in producing some symptomatic improvement in schizophrenics who do not manifest the classical target symptoms of hyperactivity and excitement. The drug is also useful in the treatment of acute alcoholic states and may sometimes be useful in the treatment of neurotic patients. Promazine may be somewhat less effective than chlorpromazine in conditions of this sort, and has the additional disadvantage of occasionally causing grand mal convulsions at dosages higher than 800 mg. per day in adult patients, a property chlorpromazine also possesses but to a less serious degree. Mepazine may not be quite as potent as chlorpromazine; however, it may cause somewhat more severe autonomic side effects, and it may elevate mood depression in some patients. The absence of adequately controlled comparative studies makes it difficult to class the above statements as anything other than preliminary qualitative judgments which may well have to be revised as more definitive evidence becomes available.

Perphenazine, prochlorperazine, thiopropazate, triflupromazine,

and trifluoperazine all appear, on the basis of uncontrolled clinical reports, to possess activity in the treatment of psychotic disturbances at least as great as that of chlorpromazine and may turn out to be more effective, particularly in the treatment of less disturbed or more chronic schizophrenic disorders. They seem to produce less sedation than does chlorpromazine; this may be a real advantage in the treatment of underactive, apathetic psychotics. They are also effective at lower doses than is chlorpromazine although it is doubtful if this in itself makes them more desirable as therapeutic agents. Perphenazine, prochlorperazine, and trifluoperazine may be more likely to produce parkinsonian side effects at clinically effective dosage levels, and these compounds also produce bizarre dystonic extrapyramidal syndromes at low dosages during early treatment in some patients. In addition, these drugs may cause an uncomfortable forced inner restlessness and discomfort which may develop into overt hyperactivity. All of these unpleasant side effects appear to respond well to antiparkinsonian medication.

Rauwolfia Alkaloids

For centuries the roots of the rauwolfia plant have been used by Indian physicians in mental illness. The plant contains a number of alkaloids, e.g., reserpine, deserpidine, rescinnamine. These compounds contain the indole nucleus and are chemically related to serotonin, 5-hydroxytryptamine. Pharmacologically, the alkaloids are very similar, and reserpine has been studied most extensively.

Reserpine alkaloid. Reserpine was introduced into therapeutics in the treatment of hypertension. Its usefulness in treating mentally disturbed patients was soon recognized. The site of action of reserpine in producing hypotension is central. Its tranquilizing action can be produced in smaller doses than are required for the hypotensive effect. It has been demonstrated in animals that reserpine will depress the behavior pattern in avoidance performance situations. Pentobarbital will depress the pattern only slightly. In numerous experiments it has been demonstrated that the action of reserpine alkaloid on the central nervous system

is quite different from the gross depression produced by the barbiturates. It involves an intensification of the inhibitory functions of the cortex. An alert electroencephalographic pattern is established and different behavioral patterns become manifest.

One of the interesting actions of reserpine in the brain appears to be the production of a biochemical change so that the cells no longer can maintain serotonin at a high concentration against a low extracellular level of the compound. Recent studies have shown that reserpine also interferes with the storage and release of norepinephrine in brain cells. These two amines obviously play a significant role in brain function, and their storage and release is modified by the administration of reserpine and other drugs. The brain enzyme monoamine oxidase is concerned with the destruction of these amines.

It is of interest that workers in the Ciba laboratories have been able to separate the hypotensive and sedative actions of the reserpine molecule. Through structural modifications, a new reserpine analogue has been prepared that exhibits primarily hypotensive activity but only one-twentieth the sedative potency of reserpine. Another analogue shows primarily the sedative action of reserpine, is prompt acting, and has less than one-fortieth the hypotensive activity. Obviously, the dual action of reserpine does not reside in one portion of the molecule, and future explorations of the pharmacology of these interesting alkaloids bids fair to yield a number of useful synthetic derivatives.

Clinical use of rauwolfia alkaloids. Although reserpine and other rauwolfia alkaloids can be effective in the control of disturbed hyperactive psychotic states, they appear to be slower to act and to be somewhat less potent in this respect than are the phenothiazines. There is a highly regrettable lack of evidence which would enable the clinician to determine whether certain types of patients or specific symptoms might respond better to these agents than to the phenothiazines. These drugs also cause parkinsonian side effects, hypotension, and some sedation.

Diphenylmethane Derivatives and Substituted Diols

Diphenylmethane derivatives. This group of drugs has been classed as the minor tranquilizers because they have been used

most extensively in anxiety and tension states. As a group, they are chemically and pharmacologically similar.

Available clinical information concerning the scope of usefulness of the diphenylmethane derivatives is not satisfactory. They have been less widely studied than the phenothiazines and reserpine, and it is difficult to describe their individual merits with assurance. While occasionally these drugs may be useful in the treatment of schizophrenic or other psychotic patients, uncon-

TABLE II
DIPHENYLMETHANE DERIVATIVES AND SUBSTITUTED DIOLS

<i>Generic Name</i>	<i>Trade Name</i>
<i>Diphenylmethane Derivatives</i>	
azacyclonol	Frenquel (Merrell)
benactyzine	Suavitil (Merck Sharp & Dohme)
hydroxyzine	Atarax (Roerig)
phenyltoloxamine	PRN (Bristol)
<i>Substituted Diols</i>	
meprobamate	Equanil (Wyeth)
	Miltown (Wallace)
phenaglycodol	Ultran (Lilly)

trolled clinical reports indicate that they may be effective in the treatment of nonhospitalized patients. These include neurotic patients cared for by the psychiatrist, and the large group of patients with varying degrees of anxiety and tension, neurotic symptoms, emotional upsets, and functional disorders commonly treated by the general practitioner.

Azacyclonol (Frenquel) is an isomer of the drug pipradrol (Meratran). Although these substances are isomeric, their pharmacological responses elicited by an action on the central nervous system are markedly different. Pipradrol increases the activity of laboratory animals. Azacyclonol depresses their spontaneous activity. The principal central nervous system action of azacyclonol appears to be the antagonism to hallucinations produced by lysergic acid diethylamide (LSD). Although the early clinical trials with azacyclonol as an antihallucinogenic agent in schizo-

phrenia were promising, subsequent clinical experiences have indicated a limited place for this drug in psychiatric practice.

Benactyzine (Suavitol) is another member of the diphenylmethane series. This substance is rapidly absorbed orally in animals and is rapidly excreted in the urine. The compound elicits strong anticholinergic activity. It produces some degree of local anesthesia. In experimental animals the agent has been shown to possess antiarrhythmic action resembling that of quinidine. The action on the central nervous system is marked in that it diminishes the response to stress in rats and cats. On the other hand, in some persons the drug produces an LSD-like effect with an alteration in time and space perception and a disturbance in body image. It appears to have a mild antidepressant activity which has been related to the association of fear and depression as compared to the relationship between anger and aggression. Anticholinergic compounds like benactyzine have been reported to reduce fear and depression, while antiadrenergic drugs reduce anger and aggression as well as deepening depressions. Although some mentally disturbed patients have improved on benactyzine therapy, the proportion of such patients showing improvement is not impressive. The drug appears to be neither a mood stimulant nor a depressant. It has been referred to as a "casualizing" drug. The precise role that it may play in mental illness has not been clearly delineated.

Hydroxyzine (Atarax) is a powerful antispasmodic. Hydroxyzine appears to produce mild sedation without loss of reflex activity. Animals under the influence of this compound exhibit lessened body movement and remain in a reposed state until disturbed. They respond promptly to various forms of stimulation. The margin of safety of the compound appears, from animal studies, to be greater than that of the generally used barbiturates.

Phenyltoloxamine (PRN) was originally introduced as an antihistaminic. It is closely related chemically to the central nervous system stimulant orphenadrine. Phenyltoloxamine has been used in the manic phase of affective psychosis. In the manic patient and the anxious neurotic, it behaves in much the same way as reserpine. Its role in the treatment of schizophrenic patients remains to be established.

Clinical use of diphenylmethane derivatives. None of these drugs has been shown to be effective in the treatment of schizophrenic states. Early reports which suggested that azacyclonol might have a specific antihallucinatory action have not been substantiated, and benactyzine is said to produce feelings of unreality and depersonalization. Large doses of benactyzine in normal subjects may produce a state resembling the action of mescaline or LSD. A few controlled studies indicate that benactyzine is sometimes useful in the treatment of neurotic conditions, and uncontrolled clinical observations indicate that azacyclonol, hydroxyzine, and phenyltoloxamine may also have this property. It is not possible, at present, to clearly state whether these compounds are more beneficial in the treatment of different types of patients than are the barbiturates or the other minor tranquilizers and nonbarbiturate sedatives.

Substituted diols. The second group of drugs, those affecting the central nervous system without an autonomic component, are substituted diols. These are meprobamate and phenaglycodol. Meprobamate has been studied more thoroughly and used more widely.

Meprobamate (Miltown, Equanil) produces a reversible flaccid paralysis of the skeletal musculature, while autonomic functions, the heart, and respiration are not significantly affected at these dosage levels. The desirable effects of meprobamate in psychoneuroses may be due to its capacity to block selectively interneuronal circuits, and to a reduction of exaggerated reflexes. The relaxation of skeletal muscle, as demonstrated in animals, may be an additional favorable component of the action of meprobamate.

Phenaglycodol (Ultran) has an anticonvulsive action with a sedative effect in rats. Phenaglycodol when administered intraperitoneally in mice evokes a reduction in spontaneous activity. Muscle weakness is present. Large doses produce unsteadiness in gait. The drug does not produce marked changes in respiration or heart rate. Monkeys become less aggressive and less fearful under the influence of the drug. The drug has been administered daily over six months without appreciable change in the intensity of its effect.

Clinical use of substituted diols. The recent detailed review

of the clinical literature on meprobamate by Laties and Weiss (4) clearly illustrates the difficulty in arriving at a reasonable appraisal of the clinical usefulness of any of the drugs in this group. Both phenaglycodol and meprobamate may have useful muscle relaxant properties and may be superior to the barbiturates in the management of neurotic anxiety; but the available evidence does not clearly prove either of these actions.

Nonbarbiturate Sedatives and Calmatives

These drugs represent a group of pharmacological agents that produce degrees of sedation varying from mild to hypnotic

TABLE III

NONBARBITURATE SEDATIVES AND CALMATIVES

<i>Generic Name</i>	<i>Trade Name</i>
captodiamine	Suvren (Ayerst)
ectylurea	Nostyn (Ames)
ethchlorvynol	Placidyl (Abbott)
ethinamate	Valmid (Lilly)
glutethimide	Doriden (Ciba)
methylparafynol	Dormison (Schering)
methyprylon	Noludar (Hoffmann-La Roche)
oxanamide	Quiactin (Merrell)

effects. These agents are not specifically effective in psychotic states, and their usefulness is limited in various neurotic conditions.

Clinical use of nonbarbiturate sedatives. As was the case with the minor tranquilizers, these compounds are reported, on the basis of preliminary clinical observations, to be useful in the treatment of anxiety and of tension states, but no adequate assessment of their real place in the treatment of psychiatric conditions is available at this time.

Antidepressives (Central Nervous System Stimulants)

The central nervous system stimulants which act upon the sensory areas in the brain are used to increase alertness, brighten the spirits, and combat mental fatigue. In this class are the

therapeutic agents caffeine and amphetamine. Recently, the drugs methylphenidate, pipradrol, iproniazid, and orphenadrine have been added to this category of agents which appear to have some favorable influence in psychotic depression. In addition, a number of recently announced compounds are apparently effective in those psychiatric conditions associated with depression and a joyless state of living.

Amphetamine (Benzedrine). This drug was introduced into therapeutics as an agent to produce shrinking of the nasal mucosa.

TABLE IV
ANTIDEPRESSIVES (CNS STIMULANTS)

<i>Generic Name</i>	<i>Trade Name</i>
amphetamine	Benzedrine (Smith Kline & French)
d-amphetamine	Dexedrine (Smith Kline & French)
deanol	Deaner (Riker)
desoxyephedrine*	many trade names
iproniazid	Marsilid (Hoffmann-La Roche)
methylphenidate	Ritalin (Ciba)
orphenadrine	Disipal (Riker)
pipradrol	Meratran (Merrell)

* Methamphetamine, U.S.P.

It is a sympathomimetic amine and like epinephrine stimulates the effector cells of the sympathetic division of the autonomic nervous system. In addition, amphetamine was observed to elicit cerebral stimulation. Small doses of amphetamine, which produce little effect upon the circulation or respiration, when administered orally evoke definite stimulation of the sensory cortex. This is manifested by an increase in mental alacrity, brighter spirits, and a mild euphoria. The individual may experience restiveness, volubility, and insomnia. As a psychic stimulant, the drug has gained much popularity in recent years. The psychic stimulation produced by amphetamine in normal individuals is generally followed by a sense of depression and fatigue. The drug frequently superimposes an excitability over a fatigue, permitting the individual to engage temporarily in mental and physical activities with more zest. It apparently does not obliterate the

system's basic need for rest. The drug is contraindicated in hypertensive individuals or those with cardiovascular disease. In anxiety states and in hyperexcitability, the drug should be avoided. Prolonged usage may give rise to hypertension, restiveness, vexation, and gastrointestinal disturbances. Overdosage may produce symptoms of sympathetic stimulation. Of special interest is the use of the amphetamines in hyperactive disturbed children (3).

The *dextro-rotatory form of amphetamine* is known as *Dexedrine*. This substance has been used to eliminate anhedonia, which in some cases appears to be responsible for nervous nibbling and unnecessary eating. The drug gives rise to brighter spirits and often concomitantly gives rise to a more positive determination to adhere to a diet of lesser caloric intake. The apparent appetite-suppressing action of this drug has stimulated a search for other compounds that may be more specific in their action and hence useful in treating obesity.

Methamphetamine, desoxyephedrine, is closely related chemically to amphetamine, and their pharmacological actions are similar. It is a potent central nervous system stimulant in animals and man.

Methylphenidate (Ritalin). Methylphenidate produces a cerebral stimulation similar to the response evoked by caffeine and d-amphetamine. Monkeys receiving this drug reveal rapid brain activity in electroencephalographic tracings. Increased motor activity is also manifested. In animals, with doses eliciting cerebral stimulation, methylphenidate produces no significant effect on blood pressure or respiration.

Deanol (Deaner) is a central nervous system stimulant. It lowers the threshold for audiogenic and Metrazol-induced seizures in rats. In unanesthetized animals, it antagonizes some of the effects of pentobarbital on the electroencephalogram. Because of theoretical concepts of the relationship between deanol's chemical nature and acetylcholine, deanol has been studied as a stimulant in chronic fatigue states and mild depression. It has also been investigated as an antidepressive drug in children with reading problems and other learning defects.

Pipradrol (Meratran) has the principal action in experimental

animals of stimulation of cerebral functions. The drug produces coordinated hyperactivity with changes in the behavior pattern. The effect is differentiated from amphetamine's psychic stimulation in that the animals do not show irritability and do not develop anorexia. Pipradrol antagonizes to a moderate degree barbiturate depression, but it is not effective against severe barbiturate intoxication. The central stimulating action of pipradrol has been studied, and the drug apparently activates the reticular substance of the upper brain stem, the subcortical area responsible for the alerting reaction. This stimulation is transmitted to the cerebral cortex as evidenced by loss of the resting pattern of the electrocorticogram; faster frequencies and a low amplitude response are characteristic of the alerting response which ensues. Workers studying this phenomenon have concluded that these changes from the resting to the alerting pattern may be the basis for the altered behavior elicited by the drug. Pipradrol appears to be a definite cerebral stimulant without an autonomic component in its neuronal action. In this respect it differs from the cerebral stimulating effect of the sympathomimetic amines.

Orphenadrine (Disipal). Orphenadrine is related to the antihistaminic drug diphenhydramine (Benadryl). Its principal pharmacological actions are anticholinergic, antihistaminic, and anti-tremor. It differs from diphenhydramine in that it elicits no soporific effect. The drug is readily absorbed in the gastrointestinal tract and exhibits a low order of toxicity. Orphenadrine was introduced originally for the symptomatic treatment of Parkinson's disease. It appears to be of some value in mitigation of the symptoms of the disease. Subsequently, the psychic activity of the compound was discovered. Some workers have placed the potency of the drug as a stimulant somewhat below that of amphetamine and its derivatives. Orphenadrine increases the activity of mice when measured in a photocell activity cage. This effect is antagonized by reserpine. In spite of its apparent stimulating properties, orphenadrine prolongs the sleeping time of mice injected with hexobarbital. The drug does not inhibit the conditioned avoidance response in the rat.

Iproniazid (Marsilid). This drug was originally introduced as

an isonicotinic acid derivative useful in tuberculosis chemotherapy. Because it produced very marked central nervous system stimulating effects when used in this condition, the drug was discarded. The elevation in mood and increase in appetite which iproniazid produced reached alarming proportions. Some patients exhibited hyperreflexia and gained weight very rapidly. In 1952, at the time these clinical observations were made, it was discovered that iproniazid was a potent inhibitor of monoamine oxidase. This enzyme inhibitory action has been pointed to as explaining the effect of the drug on the central nervous system. Monoamine oxidase inhibition may result in an increase in the free serotonin level of the brain. However, recent experiments have questioned the validity of this view.

In experimental animals, iproniazid is not acutely toxic. In chronic toxicity studies the drug does not produce significant hematologic or blood chemistry changes. Rather large intravenous doses are required to cause hyperactivity in the dog. Apparently this drug does not elicit the usual central nervous system stimulating effects in animals.

Numerous investigators have now demonstrated that iproniazid and other monoamine oxidase inhibitors exhibit a direct toxic effect on various organs if they are given in high doses to experimental animals. Hepatitis, which occurs in a small fraction of the patients receiving iproniazid, appears to be usually hepatocellular in type. The incidence of jaundice and hepatitis seems to vary in different groups of individuals, and liver function tests have been unsuccessful in demonstrating the onset of liver involvement. Large numbers of related monoamine oxidase inhibitors are being explored in an effort to discover those compounds that may be less toxic.

Clinical use of antidepressive agents. Amphetamine, d-amphetamine, and desoxyephedrine cause some stimulation and mood elevation in most normal subjects and may sometimes be useful in mild states of depression or fatigue. They are not usually effective in depressions of psychotic intensity. Amphetamine and d-amphetamine have proved of value in the treatment of children's behavior disorders. These drugs have been used success-

fully in children whose problems centered around their hyperactive, distractible, variable behavior, and who usually were handicapped by a short attention span and erratic performance. In the majority, but not all, of these children the results were gratifying.

Methylphenidate, pipradrol, deanol, and orphenadrine, on the basis of the available uncontrolled clinical studies, may not be more effective in the treatment of severe depressions than the amphetamines, though they may lack the occasionally undesirable sympathomimetic and anorexic side effects.

Iproniazid appears to be considerably more potent in the treatment of psychotic depressions, although its slow onset of therapeutic action, which varies from several days to several weeks, makes one ask whether some of the results observed may not be due to spontaneous remissions. Further, iproniazid is a drug with cumulative properties, and occasionally it produces serious toxic effects including severe postural hypotension, states of psychotic excitement, and sometimes the development of serious liver damage. It requires considerably more skill and caution in the regulation of dosage and the treatment of side effects than do most of the tranquilizers or the other antidepressive agents. It has not been shown to be as effective as electroconvulsive therapy in the treatment of psychotic depressions.

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Chapter 2

BASIC ISSUES IN DRUG RESEARCH WITH CHILDREN: OPPORTUNITIES AND LIMITATIONS OF A PEDIATRIC AGE GROUP

LEON EISENBERG

THIS, the first in what I trust will be a series of working conferences on child research in psychopharmacology, has no convenient precedent to guide its work. The call to the conference requested only that papers for the meeting stress "ideas," eschew data encoded in hieroglyphics on slides, and aim to provoke discussion. It is a simple matter to be provocative, perhaps even infuriating, but difficult to provide worth-while ideas which few possess in exportable surplus.

With your indulgence for this preliminary and, I fear, pedestrian effort, I shall order my remarks about three main topics: conceptual problems besetting psychopharmacological research in general; special opportunities afforded by studying children; and, finally, methodological problems in child psychiatry. I propose only to touch on a few aspects of each area, with the expectation that subsequent presentations will cover many of these issues more thoroughly.

Conceptual Problems

Clinical research in psychopharmacology is frequently undertaken with a commitment to a pragmatic or antitheoretical approach. The investigator sets himself the task of determining the efficacy of a drug X. He may utilize an "untreated" control or employ comparison agents Y and Z, whose action is regarded as established. He then prepares to record, in a more or less sophisticated fashion, whatever behavior his patients display. He may contend that his lack of commitment to a theory of drug and personality interaction allows him to remain an un-

biased reporter of "what happens" after drug administration. "Objective" analysis of the coded data, preferably by machine, is expected to separate the significant wheat from the random clinical chaff.

Now, no one will deny the chance element in psychopharmacology. It was an accidental observation by Hofmann that detonated research on lysergic acid diethylamide, folk medicine that placed rauwolfia in the formulary, unanticipated side effects of synthetic antihistamines that led to the phenothiazines. Examples are legion. We recall, of course, Pasteur's sage comment that chance favors, alone, the prepared mind. Nonetheless, we might agree that many of the agents of current interest, by-products of scientific investigation though they may have been, were not the intended result of planned undertakings. In this sense, pragmatism may be given its due—or, if not pragmatism, at least serendipity.

But when it is contended that clinical investigation can proceed without a theoretical commitment—or worse, should, in order to "see what happens"—then the nature of behavior research is grossly misconceived. The experimental subject emits a never-ending stream of observable items: respiratory exchange, circulatory rhythms, movements, outcries, heat, electric waves, metabolic transformations, and so on, and probably other items our present instruments do not measure. Even if every identified bit of information could be recorded simultaneously, the mechanical process of running correlations would only guarantee the obtaining of "significant" associations by the inexorable operation of the laws of chance alone. The investigator would still be left the task, no less laborious than the original undertaking, of distinguishing the meaningful from the apparent statistical significances.

Since, in fact, current instrumentation limits us to recording only certain of the emitted items, the very process of selection must be determined by some conception, implicit or explicit, of the variables relevant to the particular investigation. Moreover, the data, once they are obtained, do not magically fall into place. The search for meaning must be guided by some concept, whether it be clinical hunch or carefully elaborated theory. The

very choice of statistical methods will depend upon a judgment of the nature of the interrelationship between the variables being examined.

Obviously, then, it is simply not possible to proceed "without theory" to gather "facts." Whether stated, or implied as a given, theory circumscribes and shapes the data we obtain. It is no less obvious that we do not possess a satisfactory comprehensive theory of behavior at present. No doubt it is this unhappy state of affairs that leads the self-proclaimed pragmatist to regret the need for reliance on theory at all. This, however, misconstrues the role of theory. What is to be regretted is failure to make theoretical premises explicit so that their validity can be examined. Still more regrettable is the reliance upon circular systems which admit of no facts that cannot be "explained" in retrospect. However incorrect, a theory may still be productive if its terms are operational and its predictions subject to experimental attack. "Bad" theory is not "wrong" theory but *untestable* theory.

It is likely that an important source of the indifference to theoretical issues stems from the therapeutic orientation of the bulk of drug research with human beings. The goal is the discovery of an agent that will cure mental disease. This noble end is the most readily understood by the public and hence the most lavishly supported. However, the urge to treat, the ultimate aim of every physician, all too often is accompanied by an impatience with theory for which we are told we cannot afford to wait. I would not for a moment suggest that the empirical clinical trial be abandoned until theory is further advanced. Profit can still be obtained from sifting through exaggerated claims, contradictory results, and unproductive screening to glean the nuggets of clinical value and the rich veins discovered by good fortune. It would be a major error, however, if we did not insist upon major support for studies employing chemical agents as subtle and delicate scalpels for the dissection of behavior, to follow Claude Bernard's analogy. Such investigations, undertaken to clarify the determinants of behavior, are likely to bring us closer to the very therapeutic goals they may for the moment abjure.

Unfortunately, many current fundamental investigations are

vitiated by a tendency to reduce the causes of behavior to one class of variables: either metabolic, physiological, psychological, or social. Such an "exclusive salvationism," to borrow Adolf Meyer's apt phrase, leads to investigative blind spots for simultaneously acting variables, with the ultimate outcome of apparently paradoxical findings. Drug X may prove to be a stimulant for subject A, a depressant for B, and a stimulant for C under one set of experimental conditions and a depressant under others. This does not imply that pharmacological actions cannot be rationalized, but rather that they interact with the past history of the subject, his initial state at the time of administration, and the motivations created by the experimental procedure.

Moreover, the exclusive focus on one class of variables may be compounded still further by restricting attention to one set of factors within the class; conclusions then may be drawn about the state of individual elements within a class from observations limited to net change in the complex system itself. To take an example, when EEG changes after medication have been similar to those produced by stimulation of the reticular activating system (RAS), it has been concluded that the drug acted by stimulating the RAS. The impropriety of this deduction can be seen from the following considerations. To begin with, the RAS is, in fact, not a "system," but a system of systems. Secondly, the EEG is an algebraic sum of electrical excitations originating from many foci. Similar final effects may have their origin in quite different physiological causes. Thus, before we can establish the site of action of a pharmacological agent, direct measurement within the central nervous system is necessary. A similar warning applies to ready extrapolation from *in vitro* findings on excised nerve to actions on an intact organism. Drug Y may be an excitant on nerve *in vitro* but *in vivo* may depress behavior by preferential stimulation of a center whose physiological function is inhibitory. The simple-minded metabolic hypothesis is insufficient when it supposes that the exalted or inhibited function of brain areas should be directly reflected in overt behavior. We have already learned, somewhat painfully, that experimental lesions do not lead to behavior that is simply expressive of an additive or subtractive effect from the manipulated area, but rather lead to

behavior that represents the reintegrated activity of the central nervous system, directed toward organismic homeostasis under conditions of altered part functioning. Apparently identical end states in behavior may result from modifications in very different underlying functions. The tranquilized patient may be responding to the chemical influence of the drug he has received, to its symbolic value as a helping agent, or to the altered social organization of the experimental ward, and most likely to all three. We cannot legitimately reason from effects to causes, but must laboriously explore mechanisms, modifying one class of variables while we control for the others.

None of this, of course, is new, though the language and the methodological concerns are contemporary. It is a less elegant formulation of what Claude Bernard (4) had to say more than 90 years ago when he pointed out that "physiologists and physicians must never forget that a living being is an organism with its own individuality (p. 88) . . . must always consider organisms as a whole and in detail, at one and the same time (p. 91) . . . we must not only reckon with variations in the surrounding cosmic environment, but must also reckon with variations in the organic environment—that is to say, the present state of the animal organisms" (p. 116).

To these cautions about biological individuality, the relation of part and whole, and exogenous and endogenous variables, those of us engaged in psychological research today must add: the influence of the investigator upon what he investigates. The shibboleth of the "objective observer" glosses over the inescapable consequence of investigative procedure: the alteration of what we measure by the very process of measurement.

You will recognize in this a formulation akin to the uncertainty principle. It is nowhere more clear than in the psychological study of the human subject. The interview, whether free or rigidly structured, though designed to sample the behavior of the subject to obtain a base line, alters that base line to an unknown and unpredictable degree. What would have occurred had we not sampled the behavior, we cannot know. The less we perturb it by minimizing our measuring device, the less information we possess about its detail. The more completely

we attempt to specify initial conditions, the greater the modifications we induce in them. Only by being aware of this interaction can we take it into account by electing to sacrifice one or the other pole of the antinomy for the purpose of a particular investigation and thus approximate, where we cannot specify, the original conditions from which change must be measured.

Special Opportunities Afforded by Studying Children

What particular purposes are to be served by research with children? The answer to this question is not self-evident if we are to judge from the paucity of published work and from the avowed intent of today's conference "to stimulate further research in this area" (2).

We might begin our answer by recalling the magnitude of unmet needs in child psychiatry (11). It has been estimated that some 10 per cent of school children are in need of psychiatric care (1), a figure corresponding to rates in other age groups (21). But even if the actual prevalence should prove to be only one-half or one-quarter so great as the estimate, we would still be faced with an enormous problem in public health. Thus, any contribution to the understanding and treatment of psychiatric disorders in children would represent a major medical advance in its own right. Moreover, current psychiatric theories place heavy emphasis on the etiological role of childhood experience in determining adult psychiatric status (19). The follow-up studies of O'Neal and Robbins (20) indicate that the likelihood of disturbed children becoming adult psychiatric casualties is significantly higher than that for a classroom control group of normal children. We might therefore anticipate that improved methods for identifying, preventing, and treating childhood disturbance would help to prevent mental illness in the adult, the public health problem of our era.

It would hardly seem necessary to search further for the justification of psychopharmacological research in children. Yet, without in any way minimizing these considerations, I would add that pediatric studies may play their most significant role by affording unique avenues of approach to the understanding of human behavior. The psychic functions that are to be found fully

elaborated in the adult are nascent in the child. By analyzing drug effects at various stages of maturation, by seeking to modify interruptions in orderly development, by attempting to accelerate or retard the developmental process, we may succeed in dissecting out the determinants of behavior that, in the adult, resemble archeological ruins overlaid by the structure and the debris of successive psychological epochs.

It will be the burden of the remainder of my argument to hint at some of the special opportunities and some of the methodological problems that characterize research with children.

The central task of childhood might be defined as the orderly acquisition of a repertory of patterned behavior that will permit independent, socially constructive, and self-satisfying function in adult life. Underlying this development are two major interacting processes: biological maturation and learning. The biological potentialities inherent in genetic make-up at birth are by no means inevitable; their appearance and their rate of unfolding are subject to environmentally induced modification, but the biological given sets limits to the plasticity of the organism. What is learned begins with a series of stimulus-specific response patterns appropriate to neurological capabilities at each succeeding stage, but rapidly transcends elemental reflexes. We learn to learn. The acquisition of language permits the transformation of primitive intelligence to conceptual reasoning. At each point in this evolution, which I have grossly oversimplified and foreshortened, pathology may intervene. So may the investigator.

In working with children, the younger the child the greater the advantage we possess in the relatively brief period of prior experience that enters into the determination of current behavior. At the same time, the *tabula rasa* of the newborn is a *tabula* with its own material properties that may govern the ease with which particular signs are inscribed upon it. Recent work with autonomic reactivity in infants suggests the possibility of constitutionally determined patterns of stability and sensitivity (17, 26). The current studies of Chess and Thomas (7, 29) are beginning to provide evidence for a response typology. It would appear profitable to explore drug action with "constitutional type" as a variable, both for an independent measure of the validity of

the concept of types and for a guide to therapeutics in a given patient. If there are infants with unusual sensitivity to sensory stimulation, as Bergman and Escalona (3) have suggested, and if these infants are thereby rendered more vulnerable to traumatization, then drugs that might insulate the organism from the environment by damping input curves could conceivably confer stability. Contrariwise, the autistic child (13), who is remarkably unresponsive to at least some aspects of his environment (9), might be impelled to attend to them by drugs that amplify inner excitation, as Freedman's recent work with iproniazid suggests (15).

In the psychology of learning and of intelligence, there are exciting possibilities for investigation. Consider, for instance, the still-disputed question of the psychic costs of "tranquilization." Does the tranquilized patient pay for his symptomatic relief at the cost of lowered mental acuity and dexterity? Contradictory findings have been presented in the literature. Our failure to resolve this issue may be the result of the insensitivity of measuring devices to changes in intellectual functions in the adult. The adult possesses a ready store of previously recorded information and a repertory of problem-solving behavior. Probably both are coded in the brain with a considerable margin of safety, if we may reason by analogy from other vital organs. Hence, defects in intellectual function in the adult may be difficult to sense, particularly so since ordinary life and most test situations do not present a stressful challenge to intellectual function. The child, on the other hand, possesses a relatively small backlog of adequate precedent. His life's work is learning. A major criterion of successful adjustment for the child is scholastic proficiency in learning new material. Laboratory studies of learning following the acute administration of drugs and clinical studies of school performance during chronic drug therapy would provide methods sensitive to psychic blunting, if it does occur.

Let it be clear that the task is not a simple one. If the emotional distress which led to psychiatric treatment had been playing an important role in impairing academic efficiency, effective drug therapy, by relieving anxiety or diminishing distractibility, may result in over-all improvement in school performance, despite

any direct drug-induced decrement. But if this should prove to be the case, we would at least diminish the nagging concern over possible losses. Unfortunately, the logical control, a normal long-term drug-treated group, is not ethically warranted. However, a study of the academic performance of a control group of disturbed children treated with psychotherapy—if psychotherapy and drug therapy are equivalent as treatment—might enable us to detect any intellectual decrement that is due to the drug itself.

What may be a vexing complication in studies of learning *per se*—the interaction between emotion and intelligence—is in itself a fundamental problem for psychiatric theory. I have considered elsewhere the conceptual confusion underlying the dichotomy between feeling and reasoning conceived as polarities in psychic function (12). Our very inferences about emotional disorder are drawn from the observation of deviations in perception and rational behavior. It is the terror-stricken response to the rustle of a leaf, the inexplicable logical fallacy in the brilliant thinker, or the bizarre lapse in social behavior that leads us to search for pathological affective forces. Emotion involves the cognitive apparatus from its very onset, for it is the apprehension of the significance of the external and internal stimuli to which the organism responds that triggers the appropriate feeling tone. Rational analysis generates convictions with an emotional charge that in turn becomes a motivating factor for subsequent behavior.

The traditional metaphysical dichotomy between feeling and thinking has some of its roots in the historic separation between academic and clinical psychology. The academic psychologist has, until recently, tended to limit his concern to problems of intelligence and learning in laboratory situations, the clinician to limit his concern to emotional disturbance in the treatment situation. Each sees disturbances in the other sphere as secondary to malfunction in the area of his own interest. Yet it has become increasingly clear, from both ends of the spectrum, that learning and intelligence depend upon motivations, attitudes, and interpersonal relations, and that emotions, far from being primary instinctual phenomena alone, are learned as well.

Piaget has documented the early development of what he terms “sensorimotor intelligence” (23). The infant passes from an ap-

prehended external world of plastic images confused with sensations of a "self unaware of itself" to an apprehended universe composed of permanent objects connected by causal relations, a universe in which the *self is aware of itself* as a cause among causes. This is the border of conceptual thought. For egocentric thought, seeking its own satisfactions and molding the universe to its own needs, there now must be substituted, via the development of language, collective thought obeying common laws; that is, consensually validated thought generated by social interaction (22).

At each stage in this abbreviated version of Piaget's views, we may note terms that hint at problems in ego psychology and in socialization germane to the concerns of the psychopathologist. Piaget, from his academic studies, heralds the role of interpersonal transactions as the very crucible in which thinking is smelted from the biological ore, though he does not himself study the deviations in its evolution that may stem from imperfections in the social process.

At the same time, clinicians have been accumulating growing evidence of the gross variations in measured intelligence associated with socioeconomic background (27), perverted early experience (5, 16), and psychotic syndromes in childhood (12, 18, 25). Let us agree that the clinical findings are complex, to some extent contradictory, and subject to a multiplicity of interpretations (6, 10, 24). But, by now, enough has been well established that we must go beyond the mere recording of still more instances to an analysis of the mechanisms by which these observed deviations in intelligence can be related to the familial and broader social experiences of the child.

In our clinic, a series of investigations* is beginning with the methods of Piaget and others in an attempt to specify the differences in cognition between disturbed and normal children. Once we can measure these differences, exploration with a battery of pharmacological agents may permit further elucidation of fundamental psychophysiological mechanisms.

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Methodological Problems in Child Psychiatry

A final word about methodology may be in order. Psychopharmacological research with children possesses an important clinical asset. The availability of school information enables us to obtain an independent measure of change in behavior beyond the subjective report of the patient himself and the possibly biased opinion of his family. With the adult outpatient, concern for job security and the lack of common standards of achievement make it difficult to obtain a reliable account of work adjustment. For the child, we have a standard background of academic and social expectation against which his behavior can be assessed. The population of his classroom constitutes a readily available comparison group which, because of geographic stratification, is likely to contain built-in controls for ethnic, social, and economic variables.

We must, however, reckon with a host of unresolved methodological quandaries. Whereas the adult comes for treatment largely because of his own distress and at his own initiative, the child comes to attention because of his family's or his community's initiative. Whom, then, are we to classify diagnostically: the child, the family, the community, or all three? The lack of a commonly agreed upon system of classification has led many clinicians to forego any attempt at systematics and to employ the scrapbasket category, emotionally disturbed, which renders comparison between therapeutic studies almost meaningless. Our own study, based upon the double-blind evaluation of two tranquilizers and a placebo (8), demonstrated no significant difference between the effects of these agents, but a striking difference in outcome that varied with broad diagnostic categories: neurotic, hyperkinetic, and sociopathic.

Important questions arise around the concept of improvement in the psychological sense. When "improvement" is registered, we must ask what it means. Is the child improved in the opinion of parents and community only because he is less troublesome to others if he is in a chemical strait jacket, or do we detect improvement in his own comfort and in the efficiency of his behavior? If the improvement is substantial, to what mechanism

is it to be attributed? Is the total result explicable in terms of direct pharmacological action or has the drug, by diminishing overactivity, for example, permitted parents to be more accepting with the change in parental attitude constituting a crucial factor in the final result? In the child whose symptoms make him socially intolerable, such symptomatic relief should not be despised; though only transient in itself, it may generate a train of psychological consequences in more gratifying interpersonal transactions, which themselves may lead to a more substantial improvement in basic personality organization (14).

We must be concerned not only with what is meant by improvement, but also with the durability of improvement. There are few studies with any appreciable follow-up that might permit reliable conclusions about the long-term course of childhood psychiatric illness, either as a natural phenomenon or in response to therapy. Children change as they grow. What may be ascribed to treatment may be the result of the developmental process itself. What may appear to be a remission in symptoms may be a stage of transition to another phase of disturbance. This is not to suggest that short-term studies are not valuable, but to emphasize the crucial importance of extending the period of surveillance in order to estimate the viability of the obtained benefit.

The sensitivity of the child to changes in his environment necessitates careful search for "extratherapeutic" factors. For example, applications for treatment in every child guidance clinic increase shortly after school begins, reach a maximum during winter months, and fall off again in late spring and summer. This seasonal variation may reflect, among other factors, stress imposed by school demands on the child, school pressures on parents for referral, increase in family tensions when problem children are underfoot during short daylight hours and bad weather, changes in the availability of outlets for energy discharge, and what not. The point to be made is that comparison groups cannot be filled sequentially, but only simultaneously if we are not to run the risk of a biased outcome. A study in which one group, admitted in the fall when school pressures are increasing, was measured against a comparison group treated in the summer, when drop-outs are greatest, might be very misleading.

Child research is, of course, confronted by the host of methodological problems that beset all therapeutic studies in psychiatry: the standardization of interviews, the reliability of clinical ratings, the role of the therapist's personality, the standardization of psychological tests, criteria for the selection of controls, etc. I would only urge the importance of spelling out procedures: setting out with an explicit hypothesis, indicating how patients were selected, describing experimental and control groups as fully as possible, attempting to secure diagnostically homogeneous populations, specifying the methods for measuring change and the criteria of improvement, assembling enough cases to permit statistical analysis of results, and following them for substantial periods of time (28).

May I conclude by reiterating my conviction that psychopharmacological research with children is an area of vital importance in its own right in providing guidelines for the treatment of psychiatric illness in children and in its potentiality for contributing to the knowledge fundamental to the creation of a comprehensive theory of human behavior.

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DISCUSSION

LAURETTA BENDER

As usual, Dr. Eisenberg has given us one of his well structured and lucid presentations, covering the subject in a way that reviews for us what has happened and at the same time leaves many open questions for discussion.

He has offered us the premise that it is highly important that the research worker have theories and that these theories be based upon concepts of human behavior, or at least behavior research, and not on mental illness, that we not be seeking for cures, but rather for ways of modifying child behavior. With this I would agree in principle, since one can hardly disagree with it. I would question the idea that there are theories which all would agree are desirable and biases which are undesirable. I wonder whether one man's biases are not the other man's theories, at least sometimes. And I don't know whether one can make a pre-emptory decision between bias and theory.

I would raise the question of how theories are to be obtained. For example, even my strongly reputed biological point of view was not inherited; I have developed it with many years of experiencing, experimenting, and ruminating.

I would question whether theories can be learned, even in the way that Dr. Eisenberg has used the word "learned." Theories cannot exist in a vacuum, and I maintain that the research worker, whom we are talking about here, has to acquire his theories as he lives. It is true that one may start out in one's early days with a theory which one has adopted, perhaps learned—we could even say "inherited"—from one's teachers or people one is working with or identified with. But such a worker will not continue to be a good research worker, in my books, unless he adapts his theories to his own experience.

And furthermore, I trust the time will not come in the life experience of any good research worker—I use this "good" with hesitation because, of course, it implies values which I am not defining—when he will cease to change or modify his theories. I think it is one of the very baffling and exciting things in any field of science that our greatest masters are those who have changed their theories so fast that we have a dreadful time keeping up with them, if they have been sufficiently articulate to delineate them. Let us mention Freud, for example.

So a theory has to change to be any good, and it has to change continuously with the person using it, and with new experiences that come into his life and come into the total life of our scientific body.

Dr. Eisenberg, I was going to say, complains—maybe it is the wrong word to use, again because it implies values, and negative ones—that there is no satisfactory, comprehensive theory of human behavior. I maintain that when we have a finished, satisfactory, comprehensive theory of human behavior, then it is time to quit. There won't be anything left to do. Ours should be an on-going job. As a matter of fact, we have an awful lot of good theories of human behavior that are as complete as they should be for our way of functioning. And the degree to which various people can fit into these changing processes of theory formation will represent the degree to which they can contribute to the total body of knowledge which will never be finished.

I also think we even know more about psychiatric disease processes. We don't like to use those words. I think they should

be used. I think there is a great body of knowledge in all of these areas which we know is available, and which we are continually using. It is not always easy to be as articulate and precise in spelling these things out as Dr. Eisenberg has been. That, I will agree, is true. Nor is it possible—and this is one of the things I want to quarrel about a bit—to establish this for any one given research program. If it were, I would question the value of it immediately. But we do have a living, growing body of knowledge.

He has also given a definition of childhood, or at least, "The central task of childhood," he says, "might be defined as the orderly acquisition of a repertory of patterned behavior that will permit independent, socially constructive, and self-satisfying function in adult life."

This kind of definition also fails to fit in with my way of viewing things. I would say the central task of a baby is to be a satisfactory baby, satisfactory to himself and to the people with whom he belongs; and that babyhood is in itself a reality, a period of life, at least as important as adulthood, and that we do not grow in order to be grown up, but we grow for the sake of growing.

I would also object to his statement that we learn to learn, I would rather say that we learn for learning. In other words, I feel that all of these stages of life are on-going and important for their own sake. I do believe it is part of our present culture to have this concept that people receive training, go to college, etc., as a sacrifice for the future, and that they never have any present.

Now, I believe in the future, but I believe in the present and I believe in the past as well, and I feel that these things are all summated in the present, not in the future. It is the present time that we have with us.

I am reminded, of course, of the old question, are babies human beings? I think they are human beings when they are babies as well as when they are adult.

Dr. Eisenberg also has said that the psychic functions that are to be found fully elaborated in the adult are "nascent" in the child. I don't believe this either. I think in the child they are not

nascent, that they exist, and that they function for the child, and are never fully elaborated in the adult. Anything that becomes absolutely finite and finished—well, it is finished.

So much for theories. I believe in theories, too, but we have to grow with our theories, and we have to recognize that the only way of growth is not by waiting until we have attained the period of theories, or by trying to establish some theories which are not our own, but by functioning within the area in which we are able to function.

Dr. Eisenberg argues for better research, and undoubtedly that is the motif of this meeting. It should have a hypothesis well thought out, it should be well structured, there should be adequate controls, precision of concepts and methodology, and sufficient follow-up.

I have been of the opinion, as many of you know, that we have overstandardized our concept of research. I find it somewhat interesting that the only examples that Dr. Eisenberg gives of what has been accomplished in this particular area are neither of them structured research, but chance or accidental observations. By and large, the history of science does go along those directions. It is true that he gave us the concession that a good hunch is almost as good as a good theory. I don't know how he defines the differences between hunch, bias, theory, and hypothesis. Is it by the number of words that go into the formulation of, let us say, a hypothesis, or the age of the person who has formulated it, or the person's capacity to be articulate about it?

I would like to say just a few words now about some of my own—let me put it positively—positive concepts in these areas from my own experience. To begin with, psychopharmacology in childhood is not new by any means. We can remind ourselves of the barbiturates that have been given to babies by pediatricians for a long time, or the whiskey-sugar pacifier which was and is often used when babies are being circumcised, when they are cutting teeth, or are colicky. When I was a child paregoric was given to infants if they had colic, were cutting teeth, or merely fussing when grandmother visited.

We have to remind ourselves that anticonvulsants have been

with us for a long time and are one of our most remarkable and successful psychopharmacological agents for modification of deviate behavior. Incidentally, the first several anticonvulsants were discovered empirically with no study and no hypothetical research until their value was already well established. We now know that, with a purely clinical or trial-and-error adjustment of anticonvulsant drugs, 80 per cent or more of children with convulsions can be sufficiently "controlled," both as to convulsions and behavior, to progress satisfactorily as normal children among other normal children. I think that one cannot emphasize enough the example of anticonvulsants and what they have demonstrated for us in this particular area of psychopharmacology.

Benzedrine was first used by Bradley (6, 7) and then later by myself and co-workers (3) at Bellevue for more than 30 years. This is a drug that will do one of the things that Dr. Eisenberg asked for. In children it promotes the learning process as determined by standard achievement tests. It also has other specific actions on disturbed behavior of children. For example, it relieves excessive prepuberty sexual impulses and preoccupations (5).

And Benadryl, out of some purely casual observations, was used at Bellevue for more than ten years, both on the ward under my supervision (8) and by Silver (11) in the child psychiatric clinic. It is still one of our best stand-bys for unorganized immature behavior disorders. As an antihistamine, it is of course related to some of the so-called tranquilizers such as chlorpromazine.

Our use of tranquilizers and other psychopharmacological agents which we are now exploring at the children's unit at Creedmoor State Hospital (2, 5, 9) tends to amplify what we have known about the other drugs I have mentioned. We have, of course, hopes that we will gain further experience with various drugs or combinations of drugs so that we can modify behavior of disturbed children to the point where they can tolerate their disease and live with it satisfactorily and grow into each stage of development in a satisfactory fashion. To this extent I agree with Dr. Eisenberg that at present we cannot cure mental diseases in children and should concentrate on aiming to modify behavior. But I for one do not want to lose sight of the fact that disease

processes do exist in children. I also anticipate that psychopharmacological research will open new approaches or vistas concerning these disease processes and what can be done about them.

Dr. Eisenberg has dutifully emphasized the importance of research methodology—hypotheses, designs of research, standardization of selection of patients and of controls, testing procedures, evaluation of data, and follow-up studies. However, we cannot fool ourselves by designing standardized medical research and matching controls among human beings, especially children. I have not offered a definition of a child except to say each one is a real, complete human being at each stage of development. A baby was a baby, and a child is a child, not an undeveloped grown-up. But I would emphasize several things in children. In the first place, every child is unique. This is the nature of biological development, about which as yet we do not know enough. When we try to "match" two children, we introduce an error which we are inclined to forget later.

I would also emphasize that the living human being, at whatever age level and with whatever disease processes and reactions thereto, is relating in some kind of a social situation to other personalities. Autism, by the way, is a remarkable and positive way of relating, although we can most easily define the negative features. It is a way of living among other human beings without suffering too much anxiety from the inner pressures and lack of organization and identification.

The autistic child, in my experience, is as vulnerable to stimuli as is the child with a symbiotic mechanism, perhaps even more vulnerable, and cannot tolerate or organize external stimuli. He therefore defends himself with an autistic incrustation. There is no autistic child that is 100 per cent autistic. There are never all-or-none processes in living children. Symbiotic phenomena will exist along with autistic ones so that new experiences are absorbed and incorporated into the life pattern.

I go along with Dr. Eisenberg that we need to know the very stages of development. I would say that we need to know that early puberty is an extremely critical period in which a child may suddenly become better, although he has been disturbed all during his childhood. We need to know that the age of five

and six years, in both boys and girls, is the age of greatest disorganization, but that immediately thereafter they may organize themselves very well, especially girls (1).

We need to know these things in order to use these periods as the best time for attempting a program of therapy, considering the child, perhaps, more than the controlled research (2).

I have seen a lot of well controlled research that was very bad therapy and that also, since it was research concerned with pharmacotherapy, was bad research. I cannot conceive of how one can treat a human being in distress and call it research and try to leave out the interpersonal relationships (e.g., the doctor-patient relationships), and not control the drug dosage, and not know what is going on in the individual that is being researched.

I can conceive of two teams of workers: one knows the patient and what is being done to him, while the other team makes observations without this knowledge. The only way I know of doing this is to go back to your case history after some time has elapsed but when you know or can find out what has happened to the patient. Let somebody else who did not know the children go through your records and evaluate the data and perhaps compare this late evaluation with the original physician's early predictions (4).

I will finish by making two general comments. One is that the child is your best ally. I have yet to see a child who could talk who couldn't tell me what drug he was getting and what effect he was having from it. You cannot have controlled drugs and thus have your child fooled as to what he is getting—that is impossible.

The next best ally is the parent. The parent stops the drug when the child gets better and then tells you the child never did need the drug. In my opinion, this is the best evidence that your therapy has worked.

I am one of the old clinicians who feel that research cannot be done by pattern, it has to be done by inspiration (10).

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DISCUSSION

ALFRED M. FREEDMAN

I feel in a rather strange position after Dr. Eisenberg's very careful statement and then Dr. Bender's discussion of it. We have heard the statement of the theme and the countertheme, and one would be tempted to continue the orchestration and try to merge the two themes; however, I think that might be rather too time-consuming. Rather, I will address myself to the job for which I was brought here, discussion of Dr. Eisenberg's paper.

I think that Dr. Eisenberg is stating that it is tough to do a real job in evaluating the effect of a pharmacological agent upon

the behavior of children, and that his paper might be entitled "The Hazards and Pitfalls of Psychopharmacological Research." Anyone who has completed a research project with drugs and then has agonizingly reappraised his work is painfully aware that it is exceedingly difficult to say that a certain drug has a precise clinical effect beyond peradventure. Dr. Eisenberg illustrates this problem by describing his recent investigation in which he meticulously studied in a double-blind design the efficacy of two active drugs versus a placebo and came out with negative results. Is this conclusively to be interpreted as proving that both drugs have no effect? One would answer, "Not necessarily."

But how can one design a study that will yield the desired unequivocal answers? There are certain prerequisites that must be met. At the outset one must establish goals. There are two important goals, one of which is generally present in any such study of the effect of psychopharmacological agents. First, we are interested in the therapeutic effect. In some way we want to help the child whom we see. This is a primary goal of all of us engaged in clinical investigation. A secondary goal, but an important one, is that the drugs offer us a means of gaining new insights and understandings of the psychological and physiological functioning of a child who is disturbed and, at the same time, a means of learning more about the behavior of children in general.

The very nature of any investigation is shaped by the questions asked, and consequently by the theory that one has, whether one acknowledges it or not. The sharper our questions or hypotheses are, the more meaningful will our answers be. There is a current tendency toward research projects in which one studies everything about everything in the hope that some answers will drop out. This would appear to be "built-in serendipity."

However, this leads to the important questions of what we are going to measure and how we are going to measure it. In this area we have many serious deficiencies. We do not have enough objective means of evaluating drug-induced changes in the behavior of children. I cannot at this time go into a long discussion of the many possible methodological areas. However, I have long been impressed with the possibility that those of us engaged in

research with children could gain help and insight from people who have been doing research in the animal area. I am referring particularly to some of the operant conditioning as described by Bijou (3), Azrin and Lindsley (1), and Lindsley (5), which Dr. Long will go into later at greater length. An important effort must be devoted toward the derivation of more effective means of measuring and evaluating change so that we can more accurately understand the effect of drugs.

Further, it is of great importance not to be exclusively concerned with one class of variables in a behavioral study with drugs. We are not dealing essentially with isolates, such as perception or consciousness, but with complex patterns that interact and are dependent upon the given nature of the child, the history of the child, the alterations in the environment, the alterations in the individual, and, in general, his transactions with the total environment. Thus, while we wish to sharpen questions, we certainly do not wish to so restrict a study that the results are meaningless.

Recent work on the placebo effect has certainly been most provocative. We see that practically any effect can be obtained through a placebo, and that there are variations in the population that are significant for any investigator. The background of any individual must certainly be known, as well as his mental status and his level of anxiety.

Beecher's group (2) has studied this effect of morphine, barbiturates, and amphetamine, and has found that about 80 per cent of the population will react rather typically, but that the other 20 per cent react in the opposite direction. The 20 per cent who reacted atypically were disturbed persons, while the 80 per cent who reacted typically showed the usual adjustment patterns seen in our population. The deviant 20 per cent are just the ones that we are dealing with in any psychopharmacological study. Thus, a simple comparison of the effects of a drug on normals and on severely disturbed patients may be meaningless or require most careful interpretation. Particular caution is required when one attempts to apply knowledge of drug effects gained in one population—e.g., normals—to another population—e.g., disturbed patients.

This problem becomes greatly magnified when one is dealing with children. A child is growing and changing. His level of maturation certainly might have great importance upon his reactions to various biological agents. Children do not always respond to drugs in a fashion characteristic of adults. Further, there is the possibility that children of various diagnostic categories will react differently to different drugs.

In reviewing many studies, we have to question whether the children were sick enough to give us an accurate measure of the effect of the drug. It may well be that a certain drug may produce an effect only upon sick or disturbed children, and that it may have no effect upon the normal or usual child. One might compare this situation with that facing an investigator who would only study the effect of aspirin in children without fever. He would never discover aspirin's antipyretic effect.

Another area that Dr. Eisenberg touched upon which I think is exceedingly important is the area of learning. Many parents continually ask: "What effect will this drug have on my child's school work or his ability to develop, to acquire new knowledge?" The actual work on this, particularly with our newer tranquilizers, is scanty. Freed (4) has presented an interesting investigation on the effect of chlorpromazine on children with reading disabilities. His work suggests that chlorpromazine facilitates reading tutoring.

The social implications of any drug study are exceedingly important. Every child is a member of the family. What effect does the child's taking of the drug have on the family? First, there is the mere fact that the family knows the child is receiving the drug. This modifies the family's attitude toward the child. The parents know that "something is being done." Then the altered behavior of the child may also have a dynamic interrelationship with the remainder of the family. Let us consider the hyperkinetic child who becomes slowed down when administered a tranquilizer. He will now evoke a different response in his parents, siblings, and teacher.

Another important question is the evaluation of improvement. What is improvement? A positive or negative answer may depend upon the person answering the question and the very structure

of the question. I have seen many instances where the parents will say that a child receiving a stimulating drug has become impossible. They state that the child doesn't sleep as much as he did before and is a good deal more restless. On the other hand, the teacher will say that for the first time this child has become alert and attentive.

We may also see the situation reversed when a teacher will be happy because the restless child now dozes in class all day rather than being in constant turmoil. Who is right? And what is improvement?

If one were to quibble with Dr. Eisenberg at all, one would criticize him for not emphasizing some of the gratifications and positive aspects of pharmacological research. One of the purposes of this meeting is to stimulate further research, and one would not want everyone to become so discouraged by the hazards that all would decide to abandon the field. When contemplating many of the difficulties, one often has the feeling, "Abandon all hope, ye who enter into this avenue of research." True, we have to face the fact that this is a difficult field full of pitfalls. However, with careful planning and design, significant data can be collected.

There are two possible avenues that confront one in trying to investigate a chronic, recurrent disorder of unknown etiology with exacerbations and remission—in short, mental illness. We may try to grapple with the basic clinical problem. This is difficult, and one may become discouraged. Or one may want to focus on a very small area that is circumscribed. But however successful the study may be, it may prove to be quite irrelevant to the basic clinical problem with which we are concerned.

The ideal program is one that asks critical questions in an adequately limited area so that a study may be successfully carried through, but the investigation must be related to the important clinical problems that concern us.

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BASIC PROBLEMS INVOLVED IN THE USE OF THE NEWER NEUROPHARMACOLOGICAL DRUGS IN CHILDHOOD

REGINALD S. LOURIE

THERE IS evidence that in the Stone Age man began to poison himself and then had to look for antidotes to relieve his symptoms. Pharmacology thus is reputed to be older than agriculture. This process, chiefly aimed toward relief of symptoms, worked so well that depoisoning, detoxifying, debugging, depressing, uplifting, or just plain or fancy relieving of physical or mental symptoms has become the cornerstone for our treatment processes.

It has been only comparatively recently in our medical history that treatment of the underlying cause for symptoms is considered the soundest approach, and it is even more recently that prevention has become a part of our thinking. In the field of emotional disturbances, however, there hasn't been any effective preventive medical approach available for general use. In dealing with emotional problems, the vast majority of doctors in practice have been reluctant to go the long way around to use complicated concepts, principles, and patterns of treatment. The remarkable growth and development of the tranquilizers (as we've passed from the antibiotic pharmacological era to the tranquilizing era) is in good part due to the eagerness that the medical profession has shown to have such agents available to them in practice.

In one way it is fortunate that there has been a delay in the development of tranquilizers until recently; if they had been available sixty years ago, they possibly would have delayed by many years our progress in learning about psychodynamics. On the other hand, attempts to understand the action of tranquilizers could possibly have speeded up our acquiring information about

psychophysiological and psychochemical processes. As we learn more about their action and the effectiveness of various fractions of these drugs, we can expect that we will refine more and more their use and effectiveness.

There is no question but that the tranquilizers are here to stay in spite of the questions and warnings that have been raised about them. These questions and warnings include emphasis on the dangers of their use, the eye-closing tendencies that can result from seeking symptom relief only, philosophical questions about their place in emotional development, and the place in medicine for short cuts. Let us hope, in relation to the latter, that the appearance on the market of a tranquilizer whose name spells "nervous" backwards doesn't indicate that use of the tranquilizers will follow the pattern of the cathartics.

In our culture the tendency is not to deprive our children of the good things of life, and tranquilizers are no exception to this sometimes admirable tendency. We have been, however, as is our tradition, more careful about our children than about the adults where the tranquilizers are concerned. (In this maybe we have gone against the grain of another of our traditions—"when in troubled waters, women and children first.") Therefore, in contrast to the widespread use of tranquilizers and the resulting mass of literature on the subject, comparatively little has been written about their use in children. It is interesting, too, that where children are concerned there are more protective movements afoot. I was called not long ago by the Food and Drug Administration to get some of our thinking about a new product for infants' routine use in which a tranquilizer was combined with vitamins. In other words, there is much more reluctance to expose children to the indiscriminate use of these agents. It was apparently because of this that the first experiments with the use of these drugs in children were confined to the more bizarre and uncontrollable syndromes. Therefore it was in the mentally defective, the psychotic, the extremely overactive or acting-out child that the various tranquilizers were used. But since then, even though they have been used in a wide range of problems, there still isn't enough basic research to give us agreement as to appropriate uses and dosages, and there is little agreement on why they work

when they do, or why they don't work when they don't. However, some guideposts are available, such as papers written by some of our colleagues on this panel.

Use of Drugs in a Children's Hospital

Many problems relevant to this conference were highlighted by a preliminary survey of the use of these drugs in practice. Mrs. Mary E. Robinson, a psychologist on Dr. Layman's staff at Children's Hospital in Washington, surveyed the medical staff of a large children's hospital in one of our large cities. About 46 per cent of the physicians contacted prescribed the tranquilizing drugs, to one extent or another. Of the group that used the tranquilizers, 88 per cent were pediatricians; the 12 per cent of the nonpediatrician members of the staff who used the drugs included dentists, ear-nose-throat men, neurologists, neurosurgeons, and dermatologists. Of the 54 per cent who did not use the tranquilizers, most were surgeons, but they in turn said that when such an agent was needed they would turn the situation over to a pediatrician.

The survey showed that the drugs most widely used over any length of time were the diphenylmethane derivatives; 50 per cent of the physicians sampled used these drugs, primarily because of their wider margin of safety. Seventy-five per cent of those who used tranquilizers also used the phenothiazine derivatives, but usually for a single dose; these were used mostly for physical symptoms such as vomiting, and for restlessness and colic in babies. Sixteen per cent used the propanediol derivatives. None of them had used the rauwolfia derivatives because of reports on their side effects.

These drugs were also used for children with sleep problems and enuresis, brain-damaged children, and hyperkinetic children. An interesting use of these drugs has been before dental procedures and surgical procedures such as tonsillectomies. They have been used effectively with asthmatic children and in atopic dermatitis. However, there was general agreement that the most effective uses were in acute situational anxiety states with irritability, and in the control of such symptoms as vomiting. Chronic

anxiety symptoms and certain severe compulsive patterns were uniformly unresponsive to these drugs in practice.

The patterns of use are quite thought-provoking. These drugs were given on a short-term basis, sometimes only in one dose, often because of worries about possible side effects. Dosage was usually small. All those on the staff using these drugs prefaced description of their use of the drugs with an indication of their reluctance to use them, and universally they said, "I am of the more conservative type." Therefore, in only one case was the drug given for more than a month. Actually, the side effects encountered were minimal, possibly because of the extremely conservative use of these tranquilizing agents. There was universal concern with masking of symptoms, either physical or emotional.

Probably the most direct correlation that could be made in this survey was between personality of the doctor involved and his use of the drugs. Fortunately, we were in a position to know something of the personalities of many of these doctors. For instance, the senior attending staff almost universally avoided their use. The users were mostly the younger men, and in this group, too, there was considerable variation. We would hear comments such as, "When I first started practice and before I learned how to handle some of the acute situations I ran into, I used ten times more of the drugs than I do now." Then there is the doctor who says, "As I've gotten busier and more confident of myself and know more about pharmacology, I use ten times more of the drugs." In contrast to both of these, there is the doctor who says of the drug, "I wouldn't want to do to patients what I wouldn't do to my own child," and he refuses to use the tranquilizers. The largest doses and the most widespread use of the drugs were encountered in some of the neurosurgeons, who apparently are more comfortable with the ability of the organism, the brain in particular, to recover from insults.

Some doctors, whose attitudes reveal that they are critical of the mothers, say that mothers need the drugs more than children do, and some of the doctors actually engineer the situation so that they say to the mothers, "If you get anxious, why don't you take one, too?" Some report that mothers exert considerable pressure

to use these new drugs; some doctors can't resist this kind of pressure, while others can. So we see how the personality elements do enter into the practical use of these new agents.

Major Research Needs

As we examine the basic problems involved in the theory and the use of the newer pharmacological agents, the questions that we would want answers to seem to fall into five categories. The first includes the constitutional problems, such as where and how the drugs work in relation to central and peripheral structures. The second relates to the ways in which anxiety is relieved by the use of the drugs. The third relates to the masking problems, particularly where physical symptoms are involved, but also where emotionally based symptoms enter the picture. The fourth includes better definition of the clinical problems, the indications for use, dosages, and side effects; in other words, the rules of thumb that can be applied to the more general use of these agents in practice with children. And the fifth is the philosophical questions that have been raised about the use of these drugs, particularly in terms of what happens if anxiety is not available to the growing individual.

The first two areas are sufficiently intertwined that they might best be considered together. The structural pattern of the brain is involved in the individual's ability to tolerate and deal with anxiety. We cannot define these patterns completely, but it is possible that through the investigation of the mechanism of action of these drugs we will learn about the organism's tolerances to anxiety. It is certainly clear that there are some people who from birth can easily respond to anxiety with disorganization. For such a person the question has been raised: what is wrong with giving the organic components of the ego a lift to overcome the intensity of the anxiety, when it threatens to or does overwhelm the organism?

From another point of view, the elements that go into the making of the instinctual forces are constitutional in nature. Here, too, we have quantitative and qualitative differences between individuals. We see individuals with intense, sometimes overwhelming, instinctual drives, and the question has been raised

again: what is wrong with giving the organic components of the ego a lift to overcome this intensity?

Then again, if these instinctual and other pressures on the developing organism have resulted in a fragile, unorganized ego, it has been suggested that the drugs may not be effective in assisting this component, but can be effective in restricting the impulse so that the ego is not overwhelmed.

In other individuals with a relatively good ego capacity, what is the validity in using the drugs to help deal with a level of impulse or anxiety that on an acute situational basis temporarily floods the ego and threatens to disorganize it?

In other words, we need to define better, not only in psychopharmacological terms, what is going on when a tranquilizer is effective; we need also to define in neurophysiological and neurochemical terms what are the organic components of the ego which can thus be enabled to deal more effectively with tensions or pressures before we can answer the first two questions we raised.

If with some of the drugs the action is more peripheral and in the nature of relieving muscle spasms and tensions, are we by their use simply preventing or interrupting the vicious cycle that results from becoming anxious—namely, peripheral anxiety manifestations which, in turn, cause anxiety? Does this make the source of the original anxiety more available?

Probably one of the most fundamental questions that need to be answered is: what are we doing when we use the drug? Are we dampening the anxiety itself, or are we increasing the ability of the brain structure to deal with the anxiety? Certainly the clinical impressions are that the anxiety itself is modified or dampened. But how this is accomplished isn't clear. Do the structures involved become less vulnerable to anxiety instead? If it is the anxiety itself that is dampened and if anxiety is useful, even necessary, to the organism as a warning signal, must we not aim toward defining what level of anxiety in what kind of constitutional make-up will dictate the indications for use of these new tools that we have at our disposal?

The masking of symptoms, or maybe it is better described as the palling of symptoms, has been raised as a problem that needs clarification from several points of view. In the first place, if such

symptoms as vomiting are controlled, will these mask serious central underlying difficulties, lull everyone into complacency about a patient? Where emotional problems are involved, will this relief of symptoms deter hospitalization? There is also the question of whether such relief could be used to prepare agitated children for hospitalization, or sometimes used to give needed time for supportive help while plans are worked through or facilities made available. And where do we fit studies which show that pre-operative anxiety can be advantageous? On the other hand, the psychic components of physical illness, such as the terror of the child with severe dyspnea in croup or asthma, may profit through being relieved, since they in turn tend to exaggerate the difficulty. Here the underlying difficulty may be masked.

The fourth area—the clinical approach to the use of these drugs in children—involves the process of painstaking controls and experience with a large variety of syndromes and symptoms at various dosage levels. The conditions under which they should be used need to be defined. The actions of these drugs need to be defined better so that drugs with autonomic affinity can be used in more specific ways to deal not only with the primary, but also with the secondary, involvements induced by emotional illness. The possible combinations, then, of drugs which operate centrally and peripherally—such as relaxants and stimulants—need to be clarified and experimented with under a wide variety of conditions.

The drugs very often serve the useful purpose of helping the doctor and the parents to be less anxious about the patient's anxiety. This, too, is helpful. But we have seen that the doctor is becoming anxious about the drug instead. Possibly through clinical approaches, too, we can better define constitutional variations in individuals.

The last, but not the least, consideration of problems to be explored in this area is the philosophical one, particularly where problems of development are concerned. Questions are already being raised about what effects the prolonged use of these drugs may have on the developing nervous system. What happens to those frustrating elements of life which lead to the formation of

adequate defenses? How can an organism learn to deal with anxiety if it is spared the anxiety in the face of which it can learn?

My attention was called recently to a most provocative study along these lines. Hess (1) found that imprinting in ducklings during the critical age (12 to 17 hours) was almost impossible when a tranquilizer had been given.

In order to find the answers to the problems which face us, it would seem that we have to work out ways of defining our clinical and basic-science approaches. Does this not raise the question of whether we need to include in the clinical team settings the thinking and the active participation of the neurophysiologist, the neuroanatomist, and the neurochemist, or do we need to train a new breed of investigators who are equally comfortable in the clinical setting and in the laboratory?

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DISCUSSION

DANE G. PRUGH

I want to thank Dr. Lourie for a most stimulating set of ideas. Among other contributions, he has defined quite clearly certain areas which require continuingly critical investigation of drug effect, site and mode of action, dosage, toxic and side effects, and "masking" problems. In touching upon relevant philosophical issues, he has vividly pointed up the danger of the indiscriminate usage of tranquilizing agents, a danger which is perhaps peculiar to our North American society at this point in historical time. In this connection, I am reminded of the title, though not the content, of S. J. Perelman's recent book *The Road to Miltown*, thoughtfully subtitled *Under the Spreading Atrophy*.

It is of course easy to "view with alarm." To decry or to endorse costs nothing. It is thus as tempting and unfortunate for some observers to develop nihilistic attitudes toward drug usage as it

is for others to adopt an uncritically enthusiastic approach. In condensing my thoughts for this discussion, I shall try to avoid either extreme.

I would like first to point out several additional challenging areas for future research, in partial answer to the thoughtful question raised earlier by Dr. Freedman. Let me first underline some questions to which we have as yet no solid answers. At the physiological level, as Dr. Lourie has implied, we know very little about the direct effects of such drugs upon cellular function in the central nervous system, particularly the oxidation and related enzymatic processes involved in cellular metabolism. We know equally little of the effects of these drugs upon neuro-humoral mechanisms and other aspects of central nervous system functioning. At the psychological level, there is much to be learned about drug effects upon perceptual functions (at conscious, preconscious, and unconscious levels), with important implications for our fuller grasp of the phenomena involved in perception.

As Kubie (5) has indicated, detailed study of such effect may indirectly enhance our understanding of the central symbolic process as well as other cognitive functions, perhaps contributing ultimately as well to the further elucidation of the elusive brain-mind problem. Studies in this area may also cast light upon the phenomenon of body image, and its relationship to the sense of identity and the basic self concept. Thus, in addition to enlarging our knowledge regarding specific drug effects, of physiological and psychological nature, sophisticated investigation in these areas may carry significant theoretical implications for differing conceptual views regarding personality formation and function, especially those derived from psychoanalytic theory and learning theory. The concept of the mental apparatus may be further illuminated, for example, as may the question of drive strength, already brought under scrutiny by such studies as Koret's (4), dealing indirectly with the effect of amphetamine on the particular aspect of drive strength related to aggression.

In addition to such important implications for "basic" investigation of psychophysiological and behavioral nature, the study of tranquilizing drugs requires further elucidation on a clinical level.

Although some facts are known regarding side effects and toxic manifestations in adults, little has yet been reported in the literature in relation to such phenomena in children. Many drug studies reported have not included careful physiological studies of liver function, for example. In addition, discussions with workers currently using tranquilizing drugs on children indicate that the incidence of significant toxic effects upon the blood-forming elements is higher than the literature would lead one to believe. Time does not suffice to list the known toxic effects, such as jaundice, hypotensive crises, depression, agranulocytosis and leukopenia, convulsions, parkinsonian-like syndromes, catatonic-like states, torticollis, and others, in relation to specific drugs. As with other types of drugs, the developing physiology of the child may be responsible for toxic responses at varying age levels which are quite different from those in adults. Enough is known to warrant caution in the use of such drugs until fuller knowledge regarding dosage in children, indications and contraindications for usage, side effects, and toxic manifestations is available for each new drug.

Among other clinical challenges, the question of the nature and degree of actual pharmacodynamic effect, aside from toxic phenomena, remains to be fully clarified in relation to dosage and other variables. That a pharmacological effect exists, in greater or lesser degree, for most of the tranquilizing agents needs hardly be questioned, even by the confirmed therapeutic nihilist. The exact nature of such an effect, however, together with the extent to which it may be influenced by other variables in the therapeutic equation, requires serious investigation. Idiosyncratic responses by patients to drug administration are well known. Less frequently recognized—or at least acknowledged—is the influence upon apparent drug effect by such variables as: (a) the psychological set of the patient, including the degree of confidence in the physician and in a positive therapeutic outcome; (b) the quality of the patient-physician relationship, involving the operation of suggestion and other psychological mechanisms such as transference; and (c) the attitudes of the physician, in regard to his confidence in the drug (and in his own therapeutic capacities) and in relation to his countertransference with the patient. A num-

ber of studies (8) indicate that the same pharmacodynamically active drug may at times produce markedly varying or even contrasting effects from patient to patient or from time to time in its use with an individual patient, depending upon the weighting of some of the variables mentioned above.

In reported studies of tranquilizing agents in childhood, only occasional use has been made of experimental designs, methods of coding, or statistical analysis of data which deal with some of these pitfalls in arriving at an accurate estimation of drug effect. Clinical investigation in the behavioral area is exceedingly challenging, and significant gaps still exist in our knowledge of appropriate and effective methods of evaluation. Certain methods are available, however, and the use of double-blind designs, such as that employed in Freedman's excellent study (2), should be much more widespread in relation to studies of tranquilizing agents in children. Some sophisticated research workers in this area, notably Nowlis and Nowlis (6), have suggested the use of triple-blind designs for drug studies: this involves not only the experimenters' and the patients' lack of knowledge of the specific drug to be used, but also an absence of knowledge on the part of the experimenter of the specific behavioral effects to be expected from the use of the drug. These and other methods, such as the use of ratings by independent judges, will, if applied appropriately, help to eliminate the subjective bias of the experimenter—one of the deeper pitfalls in this type of investigation.

The remarks made so far refer primarily to the problem of research on drug effects in a hospital population, as on a children's inpatient unit. In the study of the effects of drugs upon an outpatient or ambulatory sample of patients, the complexity of the situation of course increases. As John Donne has said, "No man is an island, entire unto himself." It is axiomatic that the administration of drugs always takes place in a multiple-person field. Thus, the prescription of drugs for an outpatient child involves, in addition to the child, the parents, who ordinarily give the drug at the recommendation of the physician and whose reports on the child's behavior may influence the estimation of such effect. In addition, the multiple-person field includes other members of the family group, from siblings to grandparents in

the home. As a result of conflicting interpersonal forces among members of the family groups of disturbed children, the perceptions of a child's behavior, whether or not in relation to the use of drugs, may vary from one family member to another. Thus, reliance to any extent upon the subjective appraisal by either parent of changes in the child's behavior following drug administration is fraught with great difficulty.

Although our knowledge of such phenomena is limited, one must also be alert to the possibility that changes in the behavior or symptomatic picture of the child treated with drugs may lead to shifts in his adaptive or defensive equilibrium, involving the appearance of symptoms different from those originally presented. Such possible substitution of symptoms should be distinguished from the phenomenon of "masking" of symptoms of underlying somatic disease which Dr. Lourie wisely mentioned. In the light of this concept of adaptive or defensive equilibrium, one must be prepared to deal with the underlying conflicts which produce psychological or behavioral symptoms, in order not to exchange one symptom for another. Clinical experience has provided a number of cases in which the new symptom has been more serious than the old one, which had been removed by drugs or by other active therapeutic means, without a more etiological approach to the basic problems in adaptation.

As Engel (1) and Greene (3) have pointed out, reciprocally interactive or transactional relationships exist in the human organism at differing levels of organization, ranging from the cellular or organ system processes at the physiological level through the psychological level to the interpersonal level of organization. Spiegel (7) has discussed the reciprocal interactions which take place in a transactional sense within the field of interpersonal operations in the family group. With this broad conceptual framework, it is possible to comprehend clinical situations in which shifts in interpersonal balance or equilibrium within the family appear to produce adaptive reverberations at the psychological or physiological level in the individual member of the family group. Conversely, as clinical experience documents, effects upon the behavior of a child by drugs acting at the cellular level may have interlocking reverberations at other levels, pro-

ducing shifts in adaptive balance at the psychological level of organization in the individual and alterations in family interactive equilibrium at the interpersonal level. Thus, the successful symptomatic treatment of one individual, the child patient, may paradoxically upset a pathological and tenuously balanced family equilibrium in which parents or other family members have deep unconscious needs to work out their own problems vicariously through the disturbed behavior of the child. Instances of this type are perhaps rare and are as yet little understood. Nevertheless, caution in therapeutic intervention is indicated in cases of severe family pathology, in order not to precipitate a psychosis in another member of such a sick family through the sudden alteration in behavior of the presenting patient.

In relation to Dr. Lourie's comments regarding the potential use of tranquilizing agents in the preparation of children for hospitalization, I can only underscore his mention of the possibility that some anxiety may be necessary in order for the child to achieve a successful adaptive response. One thought might be added regarding the danger of using such drugs in such a way as to overlook the need for psychological preparation of child and parent. Although psychopharmacological agents may be used as adjuncts in such an approach, they cannot be regarded as adequate substitutes for methods of promoting discussion and successful working through of associated fears or relevant conflicts in child and parents.

Finally, I would like to applaud and share Dr. Lourie's philosophical concern about the possible dangers involved in attempts to spare the growing human organism the anxiety which may be necessary for learning. It is true that the poet Auden and others have entitled ours the "Age of Anxiety." (Other persons, coincidentally, have termed this the "Age of the Child.") Anxiety in some form, however, has always been present in human experience, and the need to develop ways of controlling and mastering anxiety represents one major challenge to personality growth. Although the eminent literary critic Lionel Trilling has wisely pointed out that creativity is not derived from conflict or anxiety alone, there may still be some need for individual creativity to respond to the spur of inner conflict or outer challenge. The

well adjusted person without conflict or tension is unlikely to be a creative one, as the philosopher Overstreet has indicated, in pointing out that adjustment is not synonymous with maturity. The widespread use of tranquilizing agents may not in itself represent a threat to individuality and creativity. The attitudes which permit and promote such overready usage may pose such a threat.

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Chapter 4

POPULATIONS, BEHAVIORS, AND SITUATIONS;
SOME ECOLOGICAL CONSIDERATIONS IN
CHILD DRUG RESEARCH

LLOYD J. BORSTELMANN

AS I UNDERSTAND the purpose of this conference, the Psychopharmacology Service Center of the National Institute of Mental Health believes that the immediate and future course of drug research with children will be better served by bringing together for interchange of ideas two groups who share a common interest in the understanding and welfare of children, but who have little active converse with each other in the course of their ordinary professional activities. On the one hand are those of us with medical responsibilities who have been stimulated by the promise of the plethora of new drugs as valuable agents for alleviation of childhood disorders. On the other are those of us whose professional responsibilities for the systematic study of child behavior are, or should be, challenged by the problems of research in this area and the potential of drugs as an experimental tool for behavior study.

In this context, my own qualifications for inclusion in the conference and the nature of my expected contribution seem to reside in the facts that I know nothing about drugs and do not work actively in a medical setting—or perhaps, to put the case more positively, in the fact that I am interested and involved in the study of child behavior in a community context. When first invited to this conference my reaction was one of delight for the opportunity to learn something of the current thinking about drug research with children, but also of hesitation as to what sort of coinage I might offer in return. At the risk of mixing metaphors or analogies, I feel in part like the boy peeking through the knot-

hole at the ball game and reporting from his limited perspective, and in part like "The Happy Warrior," the late Al Smith, whose favorite pitch from the political platform was "Let's look at the record." So with one eye on the knothole and the other on the record, I will proceed to offer some perhaps astigmatic observations.

I have been asked to raise for our mutual consideration some questions and issues relevant to the selection of subjects and behaviors in drug research and some problems of methodology and implementation inherent in the situational context of research activity. A convenient and appropriate point of departure, serving as both knothole and record, is consideration of the spectrum of children and behaviors represented in the accumulated drug research. My concern here is not with the nature of the drugs utilized nor with the evaluation of the differential effectiveness of various drugs upon various disorders, but rather with the kinds of subjects involved, the kinds of behaviors studied as relevant to drug effects upon the organism, and the problems of methodology and inference related thereto. By taking a careful look at what has been done, we may be better able to postulate areas for further inquiry.

As might be expected from recent drug developments and the rash of enthusiastic curiosity about their clinical utility, the existent literature is replete with reports about clinical trials, ranging in sample size from a few cases of a specific condition (such as tuberculous meningitis) to a few hundred cases of more general conditions such as mental deficiency. Subjects involved range in age from infancy to middle-aged defectives, whose inclusion presumably is of interest to us because of their retardation in psychological development.

Also not surprising is the typical criterion for subject selection—patients with disorders of behavior that have not seemed amenable to previous treatment conditions. Thus we find particular attention given to children with such conditions as mental deficiency, cerebral damage, epilepsy, cerebral palsy, and childhood psychosis. In addition to subjects selected on the basis of assigned membership to such diagnostic categories, there has been

understandably industrious application to those children creating serious management problems by virtue of their hyperactivity and direct expression of strong hostility.

Related to the selection of children for drug studies on the basis of clinical management and treatment are the kinds of behavior change that have been used as criteria of drug effectiveness—alteration (preferably in the direction judged as improvement) in the very behaviors central to the diagnostic identity or management problem. So in the case of mental defectives there is that ubiquitous and oft-misunderstood offspring of psychology, the IQ. With epileptics, conclusions are based on the frequency of seizures. With spastics there is attention to motor coordination. And with management problems the question is whether they are more amenable to the situational necessities of social conformity.

Finally, the studies reported to date are extremely variable in the presence of and degree of methodological sophistication, ranging from the shotgun approach with any contemporaneous change being claimed by the home team, to considerable attention to requisite experimental design in the form of carefully matched groups, placebos, and double-blind controls.

So much for the knothole view of the game in the first few innings. Now let us turn our attention to a more critical perusal of the record. My comments are not intended to derogate the wealth of clinical material that has been so eagerly and readily produced. On the contrary, as a practicing clinician who deals with childhood behavior disorders, my own experiences and on-going activities have impressed upon me the importance of clinical-trial efforts as an essential seedbed for the more fruitful hypotheses embodying the complexities of human behavior that are inevitable when attempting to cope with the realities of life adjustment. In fact, a science of human behavior based solely on the artificial situations of the experimental laboratory would produce a peculiarly biased and sterile body of knowledge. Rather, my emphasis upon the limitations of existent studies is simply intended to stress that our initial enthusiasm about drug treatment of children may not be sufficiently warranted in the

absence of more extensive, thorough, and systematic investigations. The way of science, it seems to me, is a slow, tedious, often tiresome, but at times sufficiently enlightening process. Meanwhile, our sense of clinical responsibilities is always urgent. But we must keep in mind that our basic dedication to the general course of human welfare requires that we not let our tenderhearted natures override the hard-headed attitude essential to scientific progress.

The foregoing comments are by way of introduction to my main proposition regarding the present state of our knowledge about the effects of drugs on child behavior—namely, and put in the simplest terms, that we have very little in the way of clearly established relationships that we can point to and rely upon with any degree of confidence. I must remind you that I speak without reference to the nature of drugs (of which I must plead ignorance) and with minimal attention to the nature of the disorders that have been involved in drug studies.

Situational Variables

My concern here is with our as yet limited adherence to basic principles of study design and methodology, and our inadequate cognizance of, let alone ability to control, the multiplicity of factors that may influence studies of human behavior. The first condition is understandable in the initial pioneering stage of any new area of clinical inquiry. The latter condition is the bane of the psychologist's existence and is shared by all who struggle with systematic human inquiry. Man, let alone his spawn, stubbornly refuses to be as tractable an experimental animal as the white rat. Parenthetically, even the latter personage has at times been suspected of having a mind of his own, so to speak.

Let me be more specific about the study characteristics that necessarily must leave us somewhat perplexed about the significance of the reported results and the validity of the inferred conclusions. What we have seen is a rash of strictly empirical investigation, shooting widely at whatever we could lay our hands on and were concerned about, and waiting to see if anything happened. But the way of the empiricist to the promised

land of scientific knowledge is a hard one, with stringent requirements for establishing antecedent-consequent relationships. We have had as yet little, if any, explicit recognition of the complex interactions among four factors essential to the research process—the experimental condition, the experimental situation, the organism, and its behavior.

Inevitably, introduction of any experimental condition, such as drug induction, has some effect upon the interpersonal nature of the situation. The very fact of special handling may itself produce behavioral improvement, a condition often referred to as the Hawthorne effect.

Most of you are probably familiar with the pioneering studies of the Western Electric Hawthorne plant, wherein a group of workers operating in a special experimental room for the study of variations in working conditions showed a continual increase in productivity regardless of changes in lighting, ventilation, pay methods, etc. (14). Their inclusion in the special group had, in itself, a highly significant effect upon motivation. I would suggest that similar phenomena may be operating in a clinical situation in which enthusiastic interest about potential treatment innovations creates an atmosphere of hope and confidence. With adult patients this atmosphere may produce variable reactions, depending upon their relative investments in hospitalization or discharge. With children, dependency upon parents and other authority figures, such as doctors, results in heightened sensitivity to the behavior of adults responsible for their care.

One obvious attempt to control for vitiating interpersonal effects in the case of drug studies is the well known placebo procedure with a double-blind design. However, experimental control is not assured because the side effects tend to break the shield. And placebos have been known to produce side effects as well (18). This is indeed a complex problem of experimental design.

Another notable effort to cope with the unknown contributions of situational context has been the removal of both treatment and nontreatment groups—and this points out the importance of a nontreatment control in addition to the placebo control—to a

special environment for a period prior to beginning treatment in order to establish a more adequate base line of comparative behaviors (13).

In brief substance, what I have been trying to say is that while drug administration has a seeming simplicity of experimental design, it is fraught with complications since the drug is given by one person to another in the context of a certain relationship and situation. It would seem to me that we need to have more basic research about the variables of the clinician-child relationships and the effects of hospitalization or institutionalization upon the child. We have seen something of the effects of a child upon an institution—if he gets out of hand, he gets drugs. In this connection the child's well known apprehensive dread of the needle may apply to oral medication and may produce a flight into health if he perceives that some change in his behavior may ward off the feared shot or dosage. Careful specification of antecedent conditions is essential to adequate evaluation of consequent results.

Developmental and Organismic Sampling Problems

There is good reason to suspect that the characteristics of the situational context may vary appreciably, depending upon the age and disorder of the child. We know that the interpersonal and adaptive patterns of young children differ considerably from those of adolescents. As children grow, their behavior patterns become more structured, more time-bound, and more independent. Their cognitive resources for adapting increase, but they also grow less flexible in terms of long-term consequences of environmental manipulation. How do these developmental variations interact with the structure of the treatment context? I suggest that we don't really know. And how much do we really know about the psychological concomitants of brain damage or mental deficiency in children? I would suggest that our systematic knowledge is indeed meager and that we need considerably more investigation of basic behavior functions such as perception and learning with respect to clinical disorders in children.

Here I must confess that we psychologists have been painfully lacking in interest and industry. We have only begun systemati-

cally to study the environmental context of child behavior, and for the moment we seem to be primarily fixated upon parental willingness to agree or disagree with a set of statements, such as an attitude inventory. And psychological research with childhood disorders has been notably lacking in both vigor and rigor. There are, however, some noteworthy exceptions, as in the case of recent and on-going work by Cantor and Cromwell (5), House *et al.* (9), Stevenson and Zigler (17), and others, on experimental learning studies with mentally deficient children. I suggest that such investigations of basic psychological processes in children with behavior disorders are particularly relevant to drug research. They will help to clarify the organism-behavior-situation complex into which we wish to introduce pharmacological agents and thereby enable us to be more precise in research design. Also, the experimental techniques employed therein can provide us with more objective response measures for assessment of drug effects.

What recognition has been given in drug studies to the differential effects of variations in developmental status and types of organismic malfunction? Most studies have been careful to report a breakdown of results by type of disorder, but only some have made the further essential analysis according to chronological age—namely, the interaction between age and disorder.

This brings me to the core of the problem inherent in subject selection—the representativeness of organismic sampling. Ideally, if we knew and could designate precisely the parameters of relevant intra- and interorganismic variables for a given condition of malfunction, such as mental deficiency, then we could enter into this complex armed with considerable surety and confidence about evaluating the hypothesized effects of our experimental variable. Although the monumental work of Benda and Farrell (3) on the neurophysiology of mental deficiency is a giant step toward such a goal, unfortunately we cannot reinstall the brain and resurrect the carcass for further experimental investigation. Lacking sufficient experimental control of significant factors, we must have recourse to controls based on the relative probabilities for occurrence of given behaviors under given conditions among systematically varied population samples. What I am referring to, of course, is the need for normal, non-

patient controls as well as placebo controls and nontreatment controls. I realize that I am proposing to get the drug experimenter out of the hospital and clinic and into the community, and this will present problems in terms of shifts in role perceptions and methodology. But these considerations I would like to return to later. The fact remains that we need to study carefully the effects of drugs upon the basic processes of child behavior.

One important advantage to the study of nonpatient children is that we are not committed to the remediation of certain behaviors and can devote our attention and energies to basic explorations into the psychophysiology of the whole spectrum of child behaviors. Such inquiry is essential to building comprehensive conceptions about psychopharmacological phenomena. Otherwise we run the risk of developing conceptions that are appropriate only to limited population samples. I would hope that we psychologists can entice our medical brethren into our laboratories and into the community to join in essential collaborative endeavors that should prove highly stimulating and immensely rewarding. In turn, I may coyly propose that we be seduced into sharing the stimulating and as yet minimally explored problems of psychological factors involved in the medical situation and medical customer.

So far, I have dealt principally with some of the psychological considerations inherent in experimental situations and organisms. I have not delved, nor do I propose to, into the matter of psychophysiology that is critical to the area of drug research. This I must leave to those more knowledgeable and better qualified than myself. I would simply note my understanding that there seem to be important biochemical organismic differences in this regard that must be considered (19). Are these differences related to age, disorder, experience, etc.? Again, these are questions that can be answered only by recourse to systematic investigation of the parameters involved.

Measuring Behavioral Change and "Improvement"

Leaving questions of the internal organism to others, I would like to direct our attention now to some questions about the behavioral-response side of the psychopharmacological equation.

Here I would suggest that our research efforts call for maximum ingenuity of hypotheses and procedures, while we have, in fact, been markedly hampered in vision by our concern with and fixation upon symptomatology. So we find that the criterion of behavior change has been centered more in the clinician than in the subject. We have so far relied heavily upon the clinician's observation and judgmental processes, a reliance that is central and essential to individual patient care, but one which we must be wary of in experimental inquiry. When we are utilizing the clinician as the principal measuring device, we are relying upon a procedure that is notably uncalibrated and unreliable. This has been shown repeatedly in studies designed to demonstrate and clarify the confusions of conception and communication that beset the psychiatric clinician. Ash (1) and others have found that qualified psychiatrists and psychologists show only moderate agreement in general diagnoses of identical case materials and low order agreement as to specifics of diagnostic classifications. Meehl (11) and Wittenborn (20) have discussed this problem at length. Some notable efforts (7, 8) have been made to clarify the process of clinical judgment.

I am not maintaining that the clinician is an inappropriate tool for research—far from it—but simply that we do disservice to him as an important element of the research design and consequently to the research itself unless we utilize his perceptiveness with more precision. Thus, an oversimplified statement of relative improvement will result in a rather low order of interjudge consistency when the criteria of improvement are not specified and the kaleidoscopic multiplicity of observations and cognitive inferences are actually obscured thereby. What I am proposing is that we need more thoughtful delineation of the processes involved in clinical judgment and more careful specification of the behaviors to which the clinician is to attend. Observation is a basic procedure of scientific inquiry, but it should be distinguished by establishing conditions for reliably obtaining and clearly communicating the resultant data.

One effort in this direction is noted in the use of behavior rating scales in a number of the reported studies. Unfortunately, the use of rating scales yields only the illusion of greater ob-

jectivity unless we know something of the reliability of such measures. Too often a check on the utility of the scales in terms of agreement across raters is either not done or at least not reported. If equally qualified observers cannot agree about the phenomena being viewed, then the meaning of a given observation is necessarily questionable. Rating scales present many methodological problems but these are not insurmountable, and the procedure is essential to observational methods. However, such scales are merely devices for quantifying observations, their utility deriving from, rather than being a substitute for, thoughtful consideration of the parameters of behavior to be studied and careful delineation of relevant variations within a given dimension. Rating scales have been found to be most effective when constructed in terms of concrete behavior examples. Thus, it is much easier to agree on the color of a subject's hair than on whether he wants to sleep with his mother. We must strive to find some meaningful balance between the precision of the sometimes mundanely molecular and the ambiguities of more molar, but perhaps more significant, behavioral units.

Earlier I referred to the difficulties that beset a strictly empirical research orientation. There is no adequate substitute for a theoretical formulation or hypothesis as an a priori guide in the selection of relevant variables for research. I wish that I could say that we have ample child theory in psychology to offer. However, the field of child psychology has been largely a pursuit of empirical explorations little guided or integrated by theoretical formulations. So we have been busily accumulating age norms among the fantastic arrays of child behaviors with minimal attention to integrative concepts. In fact, we have become dangerously isolated from the challenging mainstreams of psychological theory. Baldwin (2) and Radke-Yarrow (12) have pointed to the surprising failure to use children for experimental studies designed to verify and extend basic theories in psychology. There are, however, recent rumblings of discontent and alarm over this state of affairs from such hard-headed but tender-hearted individuals as McCandless (10), who has personally pursued a course of investigation designed to bridge the gap between learning theory and child behavior.

Adequate theories appropriate to the experimental study of child behavior are yet to be built. This is not to gainsay the valuable contributions of psychoanalytic theory to our understanding of children. Though time does not permit me to develop this point—or any other point—I will simply note that the Freudian theories have been found to be of immense value as clinical working hypotheses but are enormously frustrating when we attempt to reformulate them into more operational terms for purposes of experimentation (15). Although at present in psychology we can offer little in the way of child theory per se to problems of behavioral analysis in drug research, we would urge you to join with us in applications of more general psychological theories to the study of child behavior.

This digression into the closet of our own skeletons does lead me back to the perusal of the present state of affairs in the selection of behaviors as criteria for assessment of drug effects. I have already noted that we have so far been guided principally by clinical considerations, focusing upon reduction of symptomatology. I have urged that our continued use of clinical observation and judgment be guided by principles of research methodology. Refinements in clinical experimentation will result in extremely useful hypotheses for further study.

What seems to me an even more challenging and critical need is for some really creative and imaginative research into the effects of drug intervention upon the basic psychological processes of learning, perception, motivation, etc., in children who have presumably been unresponsive to the interpersonal efforts of education and treatment. A few studies (e.g., 6, 16) have incorporated some measure of learning as a criterion of relative improvement. This line of inquiry can be extensively expanded and fortified by drawing upon the accumulated knowledge and procedures of learning studies with children.

From my very limited knowledge of differential drug effects I understand that in animals some drugs have the effect of facilitating behavior while others have the converse effect of inhibiting a response (4). If so, this would seem to me to have very challenging significance for the change of behavior by new learning experiences and, on the other hand, for the stabilization

of behaviors that are more useful and adaptive. We need much more experimental manipulation on the response end of our experimental paradigm. Simply shooting and waiting will not suffice to further our cause of greater understanding and consequent improvement in patient welfare.

The Use of Nonpatient Subjects

Earlier in these remarks, in the discussion of subject selection, I stressed the need for drug studies with nonpatient groups. I would like to turn now to some consideration of the important problems of situational context that are involved in doing research with children outside a medical setting. I realize that the very notion of administering medication when a patient relationship is not involved may raise some questions of medical ethics. When subjects present themselves or are presented as patients, the physician readily assumes his role as a medical authority responsible for the patient's care with recourse to whatever treatment procedures seem appropriate, so long as they are not known to be detrimental to the patient. This last consideration may contribute strongly to hesitancy about studies on nonpatient children. It seems to me that I detect in the literature an underlying sense of uneasiness about the unknown negative effects of the drugs and a sense of relief whenever drastic, unwanted results are not apparent.

When the physician contemplates himself as functioning professionally outside a medical context, he may feel uncertain and uneasy about the appropriateness of his behavior and the nature of his responsibilities. It seems to me that in the field of preventive medicine he has a precedent for such a shift. There the physician is not faced with patient care, but rather with an essentially educative job of volunteer solicitation, as in the case of polio vaccine. What is crucially different here is that the physician must elicit a cooperative, interested, motivational state in the potential consumer. So the major problem is one of subject motivation, whether the child is dealt with in hospital, clinic, school, home, or laboratory.

Since we are interested in children, the problem is really one of parental involvement. Essential to this is an assurance that the

child's welfare will be preserved. Actually, this safeguard is probably more important to the investigator since parental confidence in the physician will tend to assume this. But how are we to convince the parent that the child needs a shot when he's not sick? Other than the fraudulent device of creating the illusion that he is sick, we must appeal to other sources of parental motivation. My suggestion would be that we emphasize not the drug aspect of the study but rather the behavior that we are interested in studying. Here we can exploit parental interest in the child's learning and behavior, but we must be quite clear about our response focus. The fact is that research may be hard to sell to an individual unless we can relate it to some interest or concern of his. An approach through the leadership of groups to which the potential subject holds allegiance has been found to be especially useful. I speak now of parents.

Thus in our own study of mental health education, involving school children and mothers, the enthusiastic commitment of the school personnel has led to unusually good cooperation from the parents. There is, of course, always the possibility of monetary return for cooperation, but this may well result in a peculiarly biased sample of children whose parents are willing to rent them to us for a fast buck. The problem of parental involvement can be a sticky one, but I believe that it can be solved by the use of considerable ingenuity and diplomacy in handling them. Otherwise, it seems to me that the problems of research are essentially similar.

In view of our insufficient knowledge of, and ability to control, drug side effects, it may be that we are not ready at this time for studies of nonpatient children. However, I would suggest that further recourse to the resources of comparative psychophysiology for experimentation with subhuman organisms will contribute considerably to our understanding of drug effects.

Summary

In conclusion, my observations about the present status of drug research with children may be summarized in terms of some perceived needs for further inquiry.

1. There is need for continued clinical experimentation with more rigorous efforts to control for situational context, organismic variations, and precision of behavioral measurement, as well as for experimental condition.

2. In addition, we are in critical need of laboratory experiments designed to elucidate the effects of drugs upon the basic processes of behavior with representative samples of both patient and normal groups of children.

3. Further, we need much more systematic study of the basic psychological processes of children with organismic disorders and knowledge about how they are similar to or different from other children.

4. Finally, we must concern ourselves with investigations of the situational contexts in which child behavior occurs.

Having started with a knothole view of the game, I may seem to have ventured boldly into the midst of the fray, trying to wield the bat and play all the other positions at the same time. If so, I must apologize for the politician in me, whose perusal of the record is notoriously slanted toward the cause which he seeks to serve. But irrespective of analogical pertinence, I hope that I have raised some issues that we may find worthy of consideration in our deliberations at this conference.

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DISCUSSION

KATHLEEN COLE

My frame of reference as a psychiatric social worker is derived from my experience in child guidance and mental hygiene clinics.

Psychiatric social workers have played an important role in child guidance and in psychiatric settings in general. The data I bring from a community clinic will, I believe, verify the need for research which Dr. Borstelmann has pointed out and add to the questions Dr. Lourie has raised.

My first contact with drugs in a community clinic that carried with it pressure from teachers and parents had to do with glutamic acid in connection with children who were not functioning adequately intellectually in school. A specific article in a popular magazine had a lot to do with this. The parents of several retarded children had read it and came to the clinic to demand this medication. This made me aware that drugs might be of some help in the treatment of children seen in child guidance clinics and also underlined the impact that articles in the lay press may have upon the community clinics.

In the 10 to 15 years since the arrival of glutamic acid, many newer and more varied kinds of drugs have been discovered and have had a more noticeable impact. The arrival of the tranquilizers or ataractic drugs has indeed posed many questions and problems. Many child guidance and mental hygiene clinics which treat children are reluctant to use drugs. They have their major contact with drugs through pressures from parents and teachers for their use or through the family physicians who have already prescribed drug treatment for children prior to referral to the clinic.

In my own experience drugs have often been tried and found not useful prior to the child's referral to the clinic. In the process of securing history data as part of the diagnostic study, I have encountered a number of children who have been suspended from school by the principal who had said the child could not be readmitted to school until a tranquilizing drug had been prescribed. In a number of other cases the family physician had already put the child on a drug. In several instances the drug was taken until the first prescription was exhausted. The parents were then advised to secure psychiatric treatment for the child since there had not been a noticeable change in the child's symptoms. In other cases the family physician or pediatrician refused to prescribe and instead suggested a psychiatric diagnostic study,

which led to a request for the clinic's services. Obviously, my experience may be considerably biased since those children whose symptoms responded well to drugs may never have been referred to the clinic at all.

In thinking about why a referral was not made to a private psychiatrist or to the clinic before drug treatment was begun, one can come up with many and varied possible answers, which may or may not be correct. First, this might have to do with fears and problems around accepting psychiatric treatment. Second, there might be the hope that drugs would give quicker results. Third, hostility toward the clinic for such things as delays in scheduling intake appointments and long waiting lists for treatment time might be involved. One could go on with this indefinitely.

Episodic data might help to show the problems and questions that arise around the use of drugs. For example, a teacher was upset because one first-grade child was hyperactive. She demanded that something be done. She arranged a talk with the family physician, who agreed to put the child on a tranquilizer. This done, the teacher became even more upset because the child was dull, sleepy, and not learning. The teacher was too anxious to call the doctor again. At this point a referral to the clinic was made. The parents were resistive toward referral but were anxious enough to keep appointments. During the time of the diagnostic study in the clinic, a conference with the family physician resulted in a readjustment of dosage. The child's behavior in school improved. The teacher became more comfortable and the parents did not follow through with the clinic's recommendations. None of the basic problems which were relevant to this child's difficulties was touched.

An obvious question arises: would it not have been better to postpone drug use until the family had become more established in a psychotherapeutic program? This may not have been possible, true, but the mother's anxiety was so great that had there not been an out, through drugs, she might have been able to become involved in a treatment program which could have had a much broader scope than just getting continued acceptance of her child in the regular classroom situation.

Another question: especially where very young children are involved, when the question of drugs for the child is raised, would it be out of order to suggest that a psychiatric diagnostic study be completed prior to the beginning of a drug treatment program? A diagnostic study in a child guidance or mental hygiene clinic covers the physical side also. If a child's problem is serious enough to warrant drug treatment, should not the source or cause be explored from all angles?

In respect to psychiatric treatment of children on drugs, I might cite a study by Mill (1) in which two children were rated for fantasy level during therapy hours when on Thorazine and when on placebo. Physical activity was slowed down when on drug, but there was no evidence to support the hypothesis that Thorazine affects fantasy in any way. There was evidence that events in day-to-day living have considerable effect in stimulating fantasy, regardless of medication used.

The use of drugs in the treatment of psychiatric disorders in children makes imperative good communication among clinic, parents, school, and family doctor. The child's behavior in school, at home, and in therapy must be known to the doctor to enable him to arrive at the optimal drug dosage. On the other hand, both the school and the family doctor must be aware of the intrafamily stresses contributing to the child's symptoms in order not to undermine the carrying out of psychotherapeutic work with the parents where this is indicated.

The use of drugs also poses a serious policy question for child guidance and mental hygiene clinics. Does the need for optimal coordination of drugs and psychotherapy justify the clinic's taking over the administration of drugs—something they have been reluctant to do in the past? More definitive knowledge about the proper place of drug therapy in the psychiatric treatment of disturbed children will be of great help to clinics in deciding how to handle this growing problem.

It is all very well to suggest, as Dr. Borstelmann has, that sophisticated studies of drug effects on, say, perception, psychomotor functions, or the learning of nonsense syllables be done; methods exist for measuring such effects. However, is it not equally important—or perhaps more important—to give detailed and

critical attention to the clinical effects of drugs as they act in the child in his natural social context—the home, the school, the community, and the mental hygiene clinic? I suggest that we need to know more about what drugs seem to be doing in such natural settings before we can decide what kinds of questions really need answering and what kinds of clinical and basic research are most seriously needed.

To take a concrete example, psychological testing is an important part of any child's diagnostic work-up in any child guidance or mental hygiene clinic. Children already on drugs are now being referred to such clinics. What kinds of alterations might drugs produce in a child's psychological test performance? How is the clinical psychologist to interpret records obtained from such children? Practical clinical problems of this sort certainly point toward legitimate research needs.

Preliminary studies like the one by Mill (1) on the effects of drugs on the behavior of children in the play therapy situation also certainly deserve extension for equally obvious reasons. Certainly, basic research is needed, but is it not also valuable to select important problems from the clinical side and to attempt to study them using whatever procedures are now available and whatever controls are now feasible, rather than waiting for the development of a perfect knowledge of normal child development or a detailed experimental validation of the apparent fact that parental attitudes influence child behavior?

Dr. Borstelmann has stressed the need for studies of drug effects on psychological functions in normal children and has suggested that school and parental cooperation for such studies can be obtained. I would like to question both aspects of his proposal. First, a drug which affects a hyperactive, disturbed child in a therapeutic manner may have either a quantitatively or a qualitatively different effect in a normal child. A study which showed Dexedrine to have an anxiety-producing effect in normal 10-year-old children might tell us nothing about its apparently tranquilizing action in emotionally disturbed hyperactive 10-year-olds. Further, even if such studies of safe drugs in normal children were scientifically highly desirable, I doubt whether school and parental cooperation would be easy to obtain. The popular re-

sponse to such scientifically rational procedures as the fluorination of water and the extreme sensitivity of parents where manipulations of their children are concerned would lead me to expect major difficulties in carrying out such a research plan.

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DISCUSSION

Fritz Redl

The criteria for selecting members of this panel had the fascinating effect that, for once in my life, frank ignorance of the topic of discussion made me eligible to participate. I am among those who were selected just because they know nothing about drugs and their effects on children. The idea apparently was that our ignorance, coupled with questions we may harbor in our minds, might induce those "in the know" to come through with statements which they might not make within the confines of their own professional groups. My task in this phase of the discussion is, of course, limited to comments on Dr. Borstelmann's excellent paper. Since some of the statements I was ready to make have already been anticipated by previous speakers, I shall confine myself to three major themes:

1. The first impression that filled my mind when I listened to some of the points made by Dr. Borstelmann was this: if we psychologists are so smart and circumspect when we tell another profession how intricate the process of measuring effects—any effects—actually is, and how poor some of the traditional approaches are when applied to complex clinical phenomena, then why don't we use that much wisdom in our own work? The fact is that psychologists face the same problems that Dr. Borstelmann listed about the measurements of drug effects, even in the study of "cleanly psychological" phenomena, and especially in studies of the effect of treatment processes. What Dr. Borstelmann warned us about, for instance, in terms of the problems of apply-

ing attitude inventories, rating scales, etc., to measurement tasks for which they were not designed is relevant not only to the study of drugs, but to investigations of any "psychological" effects on the behavior, health, and character formation of children. The same warning holds for the ability of simple "instruments" of this sort to measure progress or therapeutic effect, or the setting up of control groups, in situations where the level of sophistication and the degree of clinical relevance of a given measurement instrument or control group design are quite obviously not up to the task. I hope that our discussion will pick up this theme and clarify it further.

2. My second informal, personal impression while listening to Dr. Borstelmann's paper is related to one specific statement he made, and approaches the proportions of a feeling of panic. Dr. Borstelmann didn't seem frightened by the implications of what he suggested when he first made that statement, but I did have the impression that he became considerably worried toward the end. I felt somewhat panicky when he first said it. I am referring to his suggestions about drug research to be done on the nonpatient child.

As far as the idea in general is concerned, I agree with him, of course. Scientifically speaking, such research sooner or later will become an important issue, and there is no quarrel with such an idea on the methodological score. I would, however, like to hear more from the people who really know just what the long-range medical and side effects are, and what evidence we now have of such effects. I would especially want to know from those among us who have experience in drug research, how much longitudinal studies have revealed about the strictly body-related issue of drug use at this stage of our development. This seems especially urgent to me when I hear from previous papers and discussions in this conference that even the strictly medical practitioners seem to have problems of anxiety and guilt about the administration of drugs to some of their child patients—even where there was good reason to assume that some benefit to the patient might accrue. If physicians, on the strictly body-medical side of the picture, are still haunted by anxieties and guilt feelings, then that seems

to me a signal that we had better postpone our studies of the non-patient child.

3. My third group of remarks, stimulated by both Dr. Borstelman's and Dr. Lourie's excellent papers, and in part somewhat hinted at by them, will be directed toward the strong impression that certain basic psychological problems need to be solved if our profession is to be of any help in solving the problems of research on drug effects.

The following points might illustrate the over-all theme I am trying to underline as heavily as possible for subsequent discussion:

How do we know just what in a specific situation really produces a given specific effect on the behavior of a child? What bothers me most in all studies of effect—including those limiting themselves to strictly psychological issues—and what seems to be wrong with most follow-up studies I have seen in psychology or child psychiatry, is this: it seems to me that we usually use a very high level of clinical sophistication for our description of what the child is like while he is still with us and what "therapeutic moves" we have used to influence him. Then we suddenly drop down to an amazingly modest level of naive generalization when we ask just who did or did not become recidivist years later in an entirely different setting about which we may know little. Often we even rely on statements of untrained or biased observers to tell us how well they think our therapy did its "job."

Unfortunately, this is even true when we study the effects of measures taken while the child was still within our reach. We lack, as yet, a specific system of catching and describing all the variables that go into the impact that the momentary setting has on child behavior. As long as we do so, many of our statements about "effect" on behavior will remain rather inconclusive and open to question. It remains hard to see how we could be sure of the real nature of the effects of drugs on non-body-related behavior of our child patients beyond a certain limit, especially when we are not really in accord about just what constitutes "improvement," psychologically speaking, anyway.

In short, my general impression is that even otherwise well de-

signed psychological studies—drug studies included—have a tendency to use much too general and clinically naive criteria for the measurement of effect. We may follow a really sound description of child and therapy with the most amazing array of evaluative, normative, or naive over-all terms. Accepting the report of a nurse, an attendant, a teacher, or a parent that a child was "better" after treatment or that it benefited him seems to me a regression to a level of generality which one can hardly afford, even in the study of effects of the more well established areas of medical interventions in a child's body functions. The behavior of children is heavily influenced by the impact of the specific setting in which they operate at a given time. It seems very important to find out whether the setting in which we observe drug effects is really comparable to the behavioral setting with which we compare it. For instance, have we kept constant such factors as teacher, subject matter, specific material used in today's classroom, teacher handling, or behavior of the rest of the group that surrounds our drugged youngster at the time? Or are we simply assuming that everything we see now must be due to the effect of the given drug or its absence?

The gist of this is, if you want to measure effects that go beyond the strictly body-related data, research has to be initiated into the very methods of measuring psychological effects, drug or no drug. The methodological problems need to be taken seriously and brought to a satisfactory solution before we can promise much scientific assistance to our colleagues in the drug field. Also, the design of the study of such psychological effects needs to be as thorough, in psychological terms, and as clean of impurities as the research which led to the production of these amazing drugs must have been.

The most important issue, however, to keep in mind in all studies of drug effects seems to me the one which is related to what might be called the "psychic cost." This item becomes relevant in two directions at once.

The immediate effect of a drug on a specific function we have in mind may well be clear and readily measurable. However, what does this mean in the over-all life or treatment goals of the child? Are there other costs which are paid in terms of func-

tions that may not be as visible—or as pleasant for the adult who has to care for the child—that may be impaired in the process? Before I would be happy about the drug-produced calmness in an active child, I would like to know what happened to the underlying energy that was previously employed in the pursuit of behavior which bothered me and made me reach for the drug cabinet. Some of the behaviors which seem to suggest the use of drugs for their “calming” effects show only one side of the coin. While it leads to confusion or discipline problems, the very impulse energy that was finding discharge through overactive behavior may also constitute an important part of the child’s personality; the development and redirection of such energy might be more important than its suppression. Thus, it might be wise for quite a while to come to separate our description of just what effect the drug has on the visible parts of behavior from statements about its “beneficialness” for the child or parent.

This problem becomes even sharper when we remember that, in talking about children, we are dealing with people who undergo a most essential developmental process, the various phases of which are important and must be given an opportunity, even at the cost of considerable anxiety and discomfort to the attending adult. It seems to me that this is one of the directions in which Dr. Bender pointed with considerable emphasis. To use just one illustration, let us assume we had a drug on the market tomorrow which would eliminate the sex impulses of teenagers for four years without actually damaging the glandular and other relevant physical sex functions of the later adult years. I could certainly see how happily such a drug would be received by the present generation of adults, and also how much easier it would make life for the teenager. But, what would happen to those ego functions of an adaptive nature which also need to develop during those same years to prepare our youngster for real maturity in the psychosexual adjustment of the later adult? Where would the opportunity be, for instance, to learn gradually how to come to grips with one’s masculinity or femininity as the case may be, to develop the type of sublimations and inner defense processes that are needed for adequate control of sexual behavior in adult life? I will not mention all the other specifics of the process of

psychosexual maturation that we know so well and that certainly involve more than glandular activity alone. Ample evidence is at hand to show how tragic and dangerous an all-too-sudden emergence of full sexuality can be for a youngster whose personality is totally unprepared for the inner and outer individual and social complications of psychosexual adjustment. Would our sex-impulse-remover drug also solve those problems? Or would we pay for the relief from concern and complications during the four years of drug-induced, prolonged sexual latency by severe problems of maladjustment later? The example used was of course a hypothetical one. It was purposely overdrawn and oversimplified. I only wanted to impress you with the need to look as sharply at what will *not* happen under the influence of drugs, things that may be important to happen. The successful completion of a developmental phase is of utter relevance, in spite of the discomfort that we would like to be spared while a particular phase is in full swing.

In summary, far from discouraging rigorous research on drug effects on children, I am trying to point out a way to make it really scientific. I am concerned lest the complexity of psychological processes be overlooked or underestimated in the run-of-the-mill, surface-effect estimates so common in new research fields. I think it is the task of psychologists on interdisciplinary research teams to clean up their own backyard and to develop improved designs for studying the effect of clinically complex processes. For, after all, there is a difference between the scientifically validated use of drugs in the service of therapy, and chemical warfare against the unruly child.

THE COLLABORATIVE STUDY AS A POSSIBLE TECHNIQUE FOR CHILD RESEARCH IN PSYCHOPHARMACOLOGY

STEWART H. CLIFFORD

DR. JAMES A. SHANNON, Director of the National Institutes of Health, stated at the hearings before the Subcommittee of the Committee on Appropriations of the United States Senate: "The ability to plan and to execute vigorously large-scale investigative efforts, requiring voluntary adherence by large numbers of investigators to centrally planned research designs, is one of the major contributions of the postwar Federal medical research effort" (2, p. 662). Dr. Shannon cautioned that such collaborative programs (a) cannot be permitted to take the place of, or otherwise obscure, the individual investigator and his need for an unrestrained opportunity, and (b) that while this may be the only way to secure needed information quickly, it can easily become wasteful of resources, particularly if the premises of these programs remain essentially untested during the periods of rapid growth.

Observations on collaborative research were also made by a special group of consultants to the Secretary of the Department of Health, Education, and Welfare. Under the chairmanship of Dr. Stanhope Bayne-Jones, this group reported:

The availability of substantial research funds has made it possible to design and execute expeditiously large-scale investigations involving extensive centrally planned collaborative efforts. These research programs provide a unique opportunity to secure reliable answers, particularly in such fields as clinical evaluation of drugs and epidemiological studies.

Large-scale development research, designed to find new

drugs (as in the case of the cancer chemotherapy program administered by the National Cancer Institute), to assess known agents (as in the psychopharmacology program administered by the National Institute of Mental Health) or to determine the cause of disease (as in studies of the perinatal period administered by the National Institute of Neurological Diseases and Blindness), has expanded rapidly with the aid of NIH research grants and contract funds. Such programs generate complex administrative problems, and they raise basic policy questions of the role of government, universities, and industry. The Consultants recommended that:

Before extension of such programs above the level in the current fiscal year, intensive attention be paid to thorough consideration of the basic policy questions, to care in planning, to realistic assessment of the present state of studies of this kind, and to consideration of the effect on all medical research of absorption of resources—particularly manpower—by such programs.

As a principle, the primary resource for development and production of new drugs be the investment of private industry; and such drugs as may result from intramural research at NIH be a by-product of other studies and not the outcome of an NIH intramural drug development program (1, p. 69).

The National Institutes of Health have three active major collaborative programs: a large-scale clinical cooperative study of antihypertensive drug therapy involving a number of hospitals; a cancer chemotherapy program involving 15 cooperative clinical groups in 165 hospitals studying 44 compounds in 1,800 patients; and a collaborative five-year study of perinatal factors in the origin of the cerebral palsies, mental retardation, and other neurological disorders in 15 institutions involving 8,000 pregnancies per year.

The Psychopharmacology Service Center of the National Institute of Mental Health was organized in the fall of 1956 and in little more than a year has "established a sound organization for advising on, coordinating, and stimulating needed research in this field . . . the Center also plans to stimulate research by providing assistance and consideration to groups of scientists who may wish to conduct coordinated research in special areas" (2, p. 800). In

March, 1958, the Center's extramural program consisted of 103 research projects granted or pending, totaling \$2,311,868.

Dr. Robert H. Felix, Director of the National Institute of Mental Health, in testifying before the Senate Subcommittee stated:

At the time the Psychopharmacology Service Center was first set up, the almost unanimous opinion of the Center's advisors and of most psychiatric researchers was that not enough was known about the best methods for studying drug effectiveness in psychiatric patients to warrant the development of an expensive multihospital cooperative study of drug effectiveness. During the past year and a half the Center's extensive experience with the designing of controlled clinical trials and with the use of rating scales and other measurement devices has led to a more sanguine view of the possibilities of carrying out cooperative studies of drug effectiveness in hospitalized psychotic patients, a group for which relatively good rating procedures are now available and in which enough controlled studies have been carried out to enable a model research design to be intelligently prepared. This situation does not hold true for the depressed patient or the neurotic outpatient or for drug studies in other special areas, such as alcoholism, child psychiatry, or psychiatric illness of the senium.

The Center's Advisory Committee has recently recommended that the staff explore further the possibilities of having a productive cooperative interhospital drug study effectively organized. . . . As a general principle in the area of research stimulation, as in all research, it is evident that experience in the design of small individual studies with concurrent stimulation of improvements in methodology, is a necessary precursor of the development of larger coordinated or cooperative studies (2, p. 813).

POSSIBLE CORRELATIONS BETWEEN THE NINDB COLLABORATIVE PROJECT AND AN NIMH PROGRAM FOR CHILD RESEARCH IN PSYCHOPHARMACOLOGY

Dr. Shannon has remarked that "It is just as well, perhaps, for research programs to be set up, so that their very names (heart, cancer, mental health) serve as a constant reminder that the ultimate end of research is useful knowledge. Having served that

purpose, however, it is essential that such programs then maintain a research framework within which there is optimal opportunity for representation from and interplay among the full range of scientific disciplines and medical specialties" (2, p. 659). In the development and execution of the NINDB project, there have been innumerable occasions where the advice and cooperation of the NIMH have been enlisted.

The NINDB project is officially called a Collaborative Study of Perinatal Factors in the Origin of the Cerebral Palsies, Mental Retardation and other Neurological Disorders. The project started in 1957, and the first year was devoted to the enlistment and training of personnel, the development of the protocol, and methodology. The following institutions have joined in the program and have agreed to use a standard protocol and technique for the gathering of data for the basic study: Yale University, Brown University, University of Minnesota, New York Medical College, Medical College of Virginia, Children's Hospital of San Francisco, Children's Hospital of Philadelphia, Pennsylvania Hospital, University of Oregon, Johns Hopkins University, Boston Lying-in Hospital, Children's Medical Center of Boston, Charity Hospital of New Orleans, Columbia University, and Children's Hospital of Buffalo.

The study is anterospective in nature and has been given support for five years. Because of the low incidence of the special pathological conditions to be investigated, a total of 40,000 cases must be investigated to give statistically significant results.

During the prenatal period, the protocol will elicit information in the following areas: socioeconomic, genetic, past medical history, psychiatric, obstetric, and interval medical history. Detailed records by independent observers will give data on labor, delivery, and the condition of the infant at birth. All newly born infants in the study will be followed during their hospital stay according to the protocol; these examinations include a static and running record, a behavioral and neurological examination. Contacts with the patient will be maintained by periodic home visits by nurses or social workers. Pediatric examinations will be made at the ages of 4 months, 12 months, 36 months, and 72 months. Psychological evaluation will be made at the ages of 8 months

and 72 months. Examinations by board-qualified neurologists will be made at 12 months and 72 months. Blood serum from all mothers will be obtained and stored for viral studies. The placentas on all mothers will be studied. The numerous laboratory procedures demanded by the protocol will be performed on all patients.

Speaking from personal experience with the Boston Lying-in Hospital project, there have already been many instances where the areas studied are of interest to the National Institute of Mental Health and to the Psychopharmacology Service Center in particular.

Our project psychiatrist is conducting a one- to two-hour, tape recorded interview with pregnant women in the study soon after they register in the clinic. In cooperation with several other collaborating groups, a standard outline for the interview and a rating system are well on the way to being practical for all groups. Home visits by psychiatrically oriented social workers will follow up the psychiatric interview with a protocol that can also be evaluated for statistical analysis. It is hoped that information will be obtained that may have a correlation with the kind of labor and delivery; with a better understanding of the mother-child relationship; with a possible relation to future behavioral or developmental problems in the child; with a possible understanding of how the mother will react to an offspring with a serious malformation.

It is possible that this project may help in the solution of some of the basic problems confronting psychopharmacological research. In a study of this magnitude a relatively large number of patients will emerge requiring psychopharmacology. The existence of detailed background information that the project study should provide would assist in evaluating several questions. It would serve as a background for measuring change as the result of treatment. It would be of value in determining the influence of environmental factors. The personnel active in certain areas of this project would be in key clinical positions to make research studies in the psychopharmacological area.

Probably the most important contribution this study could make to psychopharmacological research in children is also one

of the major objectives of the project—a better understanding and more accurate classification of the diseases being studied. If a child in this study should develop schizophrenia, cerebral palsy, mental retardation, speech defects, become a serious “behavior problem,” or develop some other neurological disorder requiring therapy, there would be, tailor-made, a wealth of background data to help control the variables of environment, past experiences, and maternal attitudes.

The objective of the NINDB collaborative project is to attempt to discover the factors responsible for the occurrence of cerebral palsy, mental retardation, and other major neurological disorders. Once a child in this study is found to have developed one of these conditions, his book is theoretically closed. However, the child requires and will receive treatment. It would be wasteful of all of the useful data, laboriously obtained, on this patient were they not put to a maximum of use. It would seem to me that the Psychopharmacology Service Center might consider organizing a project to utilize this material.

I am in no position to speak for the NINDB, but I can see no reason why this amplification of their study should interfere in any way with their basic objectives.

There are other areas within the framework of the NINDB project that we are forced to consider to be psychopharmacological. What effect does chlorpromazine administered to the mother have on the fetus and newborn? We have already seen one newborn in whom we suspect that the placentally-transferred drug was responsible for extreme hyperkinesia and hyperreflexia. Our psychologists suspect that giving this drug to the mother may delay by several days the infant's peak performance on behavioral and neurological tests.

What are the effects of other types of analgesia and anesthesia on the responses and functions of the newborn? What observations should be made on the infants and children in the study who are given a tranquilizing drug for minor problems? Would it be possible to incorporate a controlled study on the indications for and effects of this therapy?

The objectives of a child research program in psychopharma-

cology have been well stated—to study drug effects on psychological functions, family relationships and community adjustments, maturational processes and central nervous system behavior; to study these effects in “behavior” problems, the organically impaired, the mentally defective, etc., and the normal; to develop research methodology and measuring instruments; to develop new hypotheses and approaches to the study of drug effects in children; to stimulate further research interest.

It would appear to me that the collaborative-study approach would lend itself to the achievement of these objectives—a long-term developmental study of drug effects in children. Coordination of this study with the NINDB cerebral palsy project might be an ancillary part of the Center’s program.

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DISCUSSION

MAURICE W. LAUFER

This is a stimulating thought of Dr. Clifford’s, and it certainly would be well if the project that he has described could be used to provide data for use in fields other than neurology. It is my understanding that all the institutions participating in the collaborative study are using a basic protocol from which no variance is to be permitted, and that there may also be ancillary studies in which all kinds of ingenious adaptations and new approaches may be used.

I would like to use one of the conditions suggested by Dr. Clifford, that of childhood schizophrenia, to point out some possible difficulties in making use of the program as it is now constituted. As you know, there are two major theories concerning the origin of childhood schizophrenia. One is that of psychogenic causation. This theory postulates that the illness stems from a particular kind of interpersonal emotional relationship, as between the parents and the child they have produced. The other major theory stresses organic causes. Essentially these theories postulate that the illness is in some way inborn or induced within the child by physical factors. A wide variety of possibilities have been suggested, including developmental aspects, brain injury (with particular reference to the diencephalon), metabolic dysfunction, etc.

The possible role of brain injury could be fairly well covered in this cooperative study. By the same token, developmental aspects could be fairly easily considered and screened. However, the standard protocol does not cover too much in the field of metabolic study, so that even if one were looking just for organic factors, something would be missing.

My particular concern, however, has to do with the possible psychological causation of childhood schizophrenia. As the basic study is organized, both the large numbers of children to be studied and the instruments required by the basic protocol pretty much emphasize a relatively superficial study of the family and the parents by the use of brief interviews, question-and-answer techniques, questionnaires, etc. These certainly are valuable in themselves and may give very much helpful information. However, it is at least conceivable that they may tend to turn up a more superficial type of phenomenon. They may not provide the information which we need and which deeper study might reveal about the role of psychological and emotional factors in the causation of childhood schizophrenia. Since adequate recording of at least some very important physical factors will be built into this study while certain important psychological data may not be obtained, results of the project might be somewhat skewed in favor of "organic" theories without having given "psychological" ones an adequate test.

This is particularly important if one figures the incidence of childhood schizophrenia at .5 per cent of the population. This in turn means that only 40 to 80 schizophrenic children per year in the whole country might fall within the group this study comprises. This is a relatively small sample, and it is of the greatest importance that it be adequately studied.

On a more positive side, the protocol conceivably could be modified for all contributing institutions to utilize the kind of observations suggested by Fish (2), which in turn are built upon those of Bender and Freedman (1), for studying the developmental status of the infant as he grows, and seeking to pick out and predict which children might develop clinical schizophrenia. This could be done without too much alteration and without altering the virtue of the basic study for developing the kinds of information for which it was originally devised.

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Chapter 6

TECHNIQUES OF BEHAVIOR STUDY FOR CHILDREN

BOYD R. McCANDLESS

IT IS REDUNDANT, because everyone in this symposium has said this, for me to say that I do not know anything about pharmacology, so I won't stress it. However, my academic knowledge of pharmacology of any sort is primarily limited to television commercials and a few fatherly and personal administrations of aspirin, Alka Seltzer, cough syrup, and mercurochrome.

But, over the last several years, I have had three personal or semiprofessional experiences that have stirred my scientific curiosity, although about these I have done nothing except wonder.

The first had to do with the middle child in a professional family that I know well. She was so frantic a baby that her parents, following the advice of their pediatrician, kept her partly sedated from birth until she was nearly a year old. Her IQ is 30-odd points lower than that of either of her siblings. Although comfortably within the national normal range (slightly under 100), it is the lowest in her class of highly selected private school children. I have asked questions about why this is. Did she experience a sort of sensory deprivation during her first year that reduced her rate and level of intellectual development or, on the other hand, is she an average youngster born to a superior family?

The second experience concerns a dentist friend of mine who has used tranquilizers on some of his most impossible child patients, six in all. Of these, five soon became "good" patients, and were subsequently treatable without tranquilizers. According to his report, they were so reinforced by this area of success in their lives that other of their behavior problems were meliorated.

The third experience concerns my second child. One night during his infancy, pushed to the brink, my wife and I tried sedation on him. The results were traumatic, since the sedation had an

effect opposite to that intended. Our pediatrician told us later that he was what is known as a "cat reactor." I have always been curious to know what behavior concomitants cat reactors have.

Because of my ignorance of the antecedent or psychopharmacological variables in this area, Dr. Fisher asked me to deal with the consequent (or developmental and behavioral) variables that may be profitable to investigate, and to discuss methods of studying them. With such a task I feel more comfortable than with psychopharmacology per se.

I shall consider techniques of research according to five standard subdivisions of child development and behavior—physical, intellectual, emotional, social, and cognitive. By cognitive I refer to the learning process.

Physical and Motor Development

The methods of studying physical growth are well charted, although perhaps not as well as we would like to believe at first blush, as has been repeatedly pointed out by Meredith (14). The necessity of studying the effects of all sorts of pharmacological agents, probably the endocrinological ones in particular, on, for example, the height, weight, strength, and coordination of children is so patent that it need not be further discussed here. However, I think we *do* need to talk about the methods of research for each of the four topics mentioned immediately above.

Height and weight are fairly easily studied, although not as easily studied as sometimes we think. On the other hand, research on strength and motor coordination in children presents knotty methodological problems. All who have thought about the subject admit that differences in motivation between boys and girls account for much of the great difference in strength between the sexes that we find from the age of about 11 on into the senium.

With reference to motor behavior, there are amazingly few adequate methods of studying or evaluating or codifying any sort of motor behavior. For example, how does one go about defining the smoothness of a motor act? Yet, I suspect any psychiatrist, psychologist, or social worker involved with problem children uses disruption of motor acts as a cue for possible disturbance, both emotional and neurological.

The coordination demanded in climbing a tree is a very different type from that involved in writing with a pencil or typing with a typewriter. The problem of defining coordination is semantically difficult. Coordination of what? Coordination for what?

None of us would deny that motor behavior and development are of great social importance. They are closely linked to many emotional and personality variables, and to the whole biochemistry of the body. But with the exception of normative information about infants and preschoolers, and studies of skills important to industrial production and competitive athletics at the high school and college level, the field of motor development and its multitude of undoubtedly important interrelationships is almost uncharted.

Almost no one except Escalona* has done much with activity level, but many of us have thought extensively about it and decided that the level of activity, so evident even at birth, may be the most important single physiological-neurological criterion for assessing the biological nature of the child that we can have. I suspect that the interaction between activity level and environment (the learning circumstances) is the thing that determines personality. We suspect this crucial interrelationship, but we have done almost nothing substantial to quantify or study it.

Intellectual Development and Behavior

As a field, the measurement of intelligence has been plowed diligently and extensively. How *well* this has been done is another thing. In any event, many plain and fancy techniques for obtaining IQ's and mental ages exist. A basic and probably universally agreed upon plank for psychopharmacological research is study of the relationships of the drugs to intellectual status and growth.

Does heavy infant sedation result in sensory deprivation and some degree of later intellectual retardation? Can tranquilizers stabilize the hyperactive or excitable brain-damaged child, such that he profits from his sensory environment rather than being overwhelmed by it, with a resultant gain in his intellectual effectiveness? Does that which inhibits motor activity facilitate verbal

* Personal communication.

and symbolic behavior (the core of our middle class, logical adjustment to life)?

Most of us agree that the neuroses and the psychoses of childhood retard intellectual growth. How effectively are they handled psychopharmacologically?

There are hints in the literature (22) that cerebral palsy children continue their mental growth for a longer period of time than their neurologically normal peers, and that intellectually retarded children without neurological damage stop growing intellectually sooner than average children. Are such trends linked to psychopharmacological agents?

The repeated routine use of standardized intelligence tests as part of psychopharmacological research is clearly indicated. Tests of special skills, of concept formation, of problem solving, and of perception also seem useful for such research.

Emotional Development and Behavior

Emotional development and behavior is my third topic. This is one of the most baffling theoretical and empirical areas of psychology, and certainly one of the most important. I would include under this heading studies of drive and drive level for the sake of convenience.

We know that psychopharmacology is closely linked to the manipulation and control of emotions and drives. I would suggest that the use of any of the techniques for studying emotion that we now regard as suggestive or hopeful is desirable. We have much information from Sears and his co-workers (19), and others, about children's fantasies in controlled and semicontrolled situations. Variations in fantasy—its aggressive and dependency components, for example—as a function either of necessary or experimental administration of drugs should be studied.

We have in the literature of the last three years at least three tests of anxiety for elementary school children, two direct (5, 21) and one projective (4). Each shows some promise in terms of having related with other variables of child behavior. We need to do much more with physiological indices of anxiety and their relationship to psychological indices. The Rorschach techniques

developed by Fisher (7) for studying the body image might be useful in drug research.

We have a rash of studies in the last few years, both with adults and children, concerning the style and techniques of handling aggression (15, 20). These appear to be profitable variables upon which to concentrate.

Considerable useful information about relationships of the self concept to other variables has come to us from studies of adults (3, 9), and self concept techniques have been used with interesting results in several studies that utilize children as subjects (8, 10, 17, 18, 24). This technique, it would appear, can be profitably explored in psychopharmacological research.

Ratings, while not satisfactory, we must refine as best we can, and continue to use. Problems in their use have been well stated at this meeting.

I suspect most of us criticize strongly the children's projective tests, but we must continue to explore them. We need to know about these tests quite aside from their possible usefulness in studying the effects of drugs. However, it is my personal impression—and some of you may disagree with this—that the projective techniques used either for therapy and diagnosis or for research with elementary school children are quite anxiety evoking. Hence, I would suggest that researchers with children should take considerable care to become not *too* projective.

For this reason, I prefer the less threatening studies of self concept, such tools as the level-of-aspiration techniques, and controlled observational and experimental methods.

Social Development and Behavior

Under this heading fall such complex concepts as competition, cooperation, conforming behavior, rebellion, how a youngster reacts to motivation in private as opposed to publicly, the social acceptance or rejection of children, leadership and followership, behavioral contagion, prestige, and conflict.

I am at present convinced—but open to argument—that the best single measure of a child's "general adjustment," regardless of how you define it, is the nature and degree of a child's acceptance by his intimate peer group (11).

In the last couple of years, we have made great progress with the problem of measuring a child's social acceptance during his early preschool years. We can get reliable and useful (or valid) measures of how well a child is accepted by his peers as early as three years of age (6, 12). These measures become increasingly reliable and stable as the child goes through life. I should say that they can play an important part in psychopharmacological research. They are easy to administer, they are cheap, they are reliable. They can be done in groups when skilfully used. They are relatively nonthreatening to children.

Related to them are the Buddy ratings. These have been profitably used by research workers in the armed services, in industry, and in the public schools. An example of a Buddy rating, designed to tap leadership, is one from a recent study by Allen and Masling (1): "Point to the children who have the best ideas for things to do, games to play, songs to sing, and things like that." The child who is the subject of the investigation has available to him pictures of all the children in his class. These pictures are mounted on a white piece of plyboard.

The validity or usefulness of Buddy ratings or Guess-Who techniques has been repeatedly demonstrated. I believe we should utilize this technique as an easy, practical tool in the evaluation of social changes that may accompany drug changes.

From the traditional literature of child development we find all-too-frequently-unused standardized, semistandardized, and free techniques for the measurement of such classes of behavior as nervous habits, interaction during free play, competition, dominance, conflict, and dependence. All of these may be important dependent variables in the pharmacological-behavioral variable that is our common concern.

Cognitive Development and Behavior

With respect to cognitive behavior and development, a most respected colleague of mine, Spiker (23), has recently said:

No matter how one views the child, one of the most obvious phenomena which occur during childhood is learning. It is just as obvious as increase in bodily size, yet it is one of the

most neglected areas of study. . . . For the control of the development of personality, character, and other behavior of children, society is largely dependent upon teaching or causing children to learn.

I suspect that none of us would quarrel with this statement, and I believe it extremely important to make traditional and applied, as well as experimental and theoretical, measurements of children's learning. From the age of six years, academic achievement is a universally present part of the day-to-day, month-in-and-month-out activities of all children in the United States, from the high-grade mentally retarded level through the upper limits of the intelligence range.

Certainly, social and emotional adjustment are intimately connected to academic achievement, and in most cases poor adjustment interferes with rather than facilitates academic learning (although undoubtedly there are neurotic children who compensate by overachieving in academic learning at the sacrifice of other aspects of their development). We possess, fortunately, traditional educational and psychological measurements of school achievement that are numerous and, within certain broad limits, quite satisfactory.

Attempts to study the elements and processes of discrimination, and mediational and symbolic learning, particularly with very young children, have been severely handicapped until recent years by the lack of methods and apparatus suitable for the use of children younger than the conventional school ages. We have a recent, very fortunate resurgence (or upsurgence) of people interested in techniques of studying learning in the very young. People such as Bijou and his students (2, 16) have given us designs for relatively economical and efficient apparatus adaptable for children from 1 year to 18 months of age and older through the childhood range. With such apparatus we can hopefully attack the important problems in this area, such as the learning-to-learn concept that Dr. Eisenberg stressed, motivation, the effects of amount and type of reward, different types of reinforcement pattern, attention span, retroactive and proactive inhibition, and the effects of the stimuli with which the child

is confronted. These endeavors are not easy, but in the last four or five years, for the first time, they are feasible.

At the Child Welfare Research Station, we are working on research in stimulus generalization. You are all aware of the fact that there is a moderately advanced theory (the demonstration of which is fundamental if Freudian theory is to be considered sound) that emotionally disturbed children are overgeneralizers: i.e., a *single* experience of theirs fans out into their whole life to a degree greater than for normal children.

The notion that high-drive children (such as those under stress or children who are victims of anxiety) are wider generalizers than children under less stress has also gained considerable currency. There is evidence to indicate that generalization in an unstructured situation (such as when we are strangers, and when we don't know what we are doing) is wider than when we know precisely what we are doing, or when we are in familiar circumstances.

The corollary of that is that stimulus generalization is wider for younger than for older children. Certainly this is a necessary assumption for postulating the paramount importance of early childhood experience for later personality development. These hypotheses about stimulus generalization have not been tested, except for one study which indicates that early primary school youngsters generalize more widely than later elementary school youngsters (13). The importance of this dependent variable in psychopharmacological research is obvious.

Summary

This presentation has been made for propaedeutic reasons only. It is helpful to look in a classificatory way (even the most elementary classification, such as the one made here) at the dimensions of children's behavior that may profitably be studied as dependent variables in psychopharmacological research. Certain areas such as physical growth and intellectual measurement can more easily, although probably not more profitably, be studied than others. The problems of measurement in emotional development are perhaps the most difficult of those mentioned.

Fairly good techniques exist for the study of important but relatively neglected areas of research such as children's learning, and motor and social development and behavior.

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DISCUSSION

EMMA M. LAYMAN

Dr. McCandless has done us a service in pointing out some specific aspects of child behavior and development which might be considered as dependent variables in psychopharmacological research, and in reviewing some of the tested methods and techniques which can be used in assessing the effects of drugs on children.

Dr. McCandless indicates that the variables which he lists and discusses were not selected or grouped on the basis of any particular theoretical orientation. However, both in his introductory remarks and in the organization of his material, he has

hinted at a concern or orientation which seems to me to be very important. He seems to imply what has been suggested also by some of the other speakers—that in studying the effects of drugs on children we should be concerned with the ways in which these agents affect the child's *developmental patterns*. In clinical work with drugs administered to adults, the chief concern has been with the alleviation of symptoms, rather than with the influence of drugs on development. If a drug administered to a psychotic adult can cause him to function as well as he did before he became psychotic, it is considered a successful therapeutic agent, even though the individual may not exceed his premorbid level of functioning. However, the young child is far from having reached his maximum potential. Hence, in drug research involving children it seems that the focus should be on the effect which drugs have on the developmental process. This suggests that we should perhaps be thinking in terms of longitudinal studies which, in addition to giving information concerning the effect of drugs on development, would also throw light on the question of whether reported changes resulting from drug administration are stable or reversible.

For convenience in discussing his material, Dr. McCandless has organized his comments around a simple classification of developmental and behavioral areas within which it is possible to assess children. His remarks about methods and techniques of assessment would be equally pertinent if some other type of classification were used. For example, if we were to think of child development within the conceptual framework of the psychoanalytic point of view, we would find that we had available tools for evaluating the effect of pharmacological agents on the strength of id impulses, on anxiety, or on various aspects of ego development. We might find ourselves a little short of adequate techniques for assessing in measurable terms the integrative and defensive aspects of the ego, but even here the difficulties are not insurmountable.

Dr. McCandless' review has pointed up some areas in which we need to develop better measurement techniques than we now have available. Of particular concern to those interested in research in psychopharmacology is the difficulty in objectively

evaluating the child's activity level, for testing the usefulness of drugs in the treatment of hyperactive children has been a major research interest of those exploring in this field. The lack of adequate techniques for evaluating hyperactivity has also been a handicap in studying the relationships between hyperkinesis, cerebral dysfunction, autonomic functions, distractibility, and learning disturbances. In infant research the stabilimeter has been used in studying activity levels of neonates (4), and it is possible that the principle of the stabilimeter could be applied in other settings to evaluate hyperactivity in older children. Also, animal research has shown that observations can be quantified and used as a basis for assessing activity level (1). Nevertheless, improved techniques are needed to make adequate studies in this very significant area.

Evaluation of motor coordination would seem to be highly desirable in studying the effects of drugs, since incoordination is associated with emotional disturbance as well as with brain damage, and motor skills are tied in with social status in childhood. Dr. McCandless' comments about the difficulties in assessing motor coordination reminded me of some studies on rate and rhythm in relation to motor skill which were made in the years between 1895 and 1930 (2, 5, 6, 8, 9). The results of these studies pointed to two conclusions: (a) that the natural rate and rhythm of the individual and the rhythm of the activity are related to motor skill, and (b) that optimal coordination occurs when activity rhythms are synchronized with the natural or preferred rhythms of the individual. Possibly one approach to the assessment of motor coordination would be that of measuring changes in bodily rates and rhythms and changes in the accuracy of rhythmic performance. Techniques for such assessment are available and easily applied (9, 10). Another approach to the study of motor coordination lies in the application of movement analysis techniques developed by Stetson (11) in the Oberlin psychological laboratory and described by Hartson (3). In this approach smooth coordinations are thought of as those involving a maximal employment of ballistic movements rather than a predominance of fixation movements. These types of movement analysis techniques perhaps could be used to quantify some of

the qualitative aspects of motor coordination so as to use them as dependent variables in psychopharmacological research.

The question of the possible relation between sedation, sensory deprivation, and intellectual retardation certainly should be studied. In this connection I wonder if we shouldn't seek to measure directly the child's reactivity to sensory stimuli. In considering the possibility that sensory deprivation results from taking certain kinds of drugs, it is perhaps pertinent to recall some of the research which has indicated a possible relation between sensory deprivation and emotional deprivation (e.g., 7).

In considering the possible effects of pharmacological agents on learning, I am wondering about their possible effects on the child's ability to relearn—to modify previously learned concepts and patterns of behavior. This type of relearning occurs in psychotherapy, as the therapist helps the child to relearn in such ways as to correct the false or distorted concepts that have been developed as the result of past learning experiences. Standard techniques for studying the learning process could be readily adapted to the experimental assessment of this kind of relearning.

Dr. McCandless mentions some of the physiological tests of emotional reactions. Perhaps if we are to fully understand the effects of drugs on children, we should do other physiological studies and use as dependent variables the results of EEG's, basal metabolic rates, pulse and respiration rates, and perhaps blood chemistry studies.

Only semifacetiously, pediatricians have talked of administering drugs to parents as a means of reducing anxiety in children. On the theory that improvement in the behavior of the child may be reflected in the anxiety and attitudes of parents, I suggest that we might, as dependent variables, study changes in anxiety and attitudes of parents.

In talking with psychologists who are involved in studies of hospitalized schizophrenic adults treated by drugs, I have heard repeated reports to the effect that the patients improve in their behavior on the ward and many of them make fairly good adjustments in the community, but frequently their Rorschachs look as schizophrenic as ever. Had their ability to adjust been judged

on the basis of projective material and laboratory studies alone, they probably would never have been released from the hospital. Dr. Eisenberg, Dr. Borstelmann, and Mrs. Cole have all implied that adequate evaluation of behavioral changes in children requires extending our operations from the laboratory and clinic into life situations. We recognize that any adult who is involved with a child will react to that child in terms of a bias, and this applies to teachers as well as parents. Nevertheless, information can be elicited in such ways as to minimize the effects of bias, and valuable material may be obtained from both parents and teachers. We also recognize the limitations of rating scales. But the use of trained observers in both free and controlled situations, in school, play groups, the doctor's office, and even in the home can provide data to supplement our laboratory and clinical findings to give us a more complete and realistic picture of the child's functioning.

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THE USE OF OPERANT CONDITIONING TECHNIQUES IN CHILDREN

EUGENE R. LONG

THE PURPOSE of this paper is to describe operant conditioning procedures which can be used in the study of child behavior. I shall attempt to differentiate these procedures from others used in child research and to indicate their sensitivity to the manipulation of a number of independent variables. In addition, I shall try to illustrate the potential usefulness of the child as an experimental organism.

The Operant Technique

Much of human behavior seems to be constituted by what Skinner calls operant responses (13). Operants correspond to the layman's "voluntary responses" in that they seem to be emitted, rather than elicited by specifiable stimuli. In addition, they have the important characteristic of operating on the environment to produce stimulus changes which feed back to the organism. Some of these response-contingent consequences have the property of increasing the probability of responding. These are called reinforcers.

Operant techniques, i.e., experimental procedures for increasing or decreasing the probability of such behavior, have long been employed with infrahuman organisms. In recent years their frequency of use with humans, principally adults, has increased (1, 9, 10, 11, 12, 15). As yet, however, only a few investigators have employed them with children (2, 3, 4, 5, 7, 8). The reason for this, perhaps, is that they are based on aims and procedures which differ from those which are usually employed in child research. For example, the purpose of operant research is to study probability of behavior and to determine those independent var-

iables which influence it. This entails selecting a convenient bit of behavior, carefully specifying its characteristics or topography, and then studying its probability by observing its frequency of emission in time under certain specifiable circumstances. In many ways this is not a new experimental tack. Skinner (14), for example, has pointed out that probability and frequency underlie many present psychological concepts, such as instinct, attitude, habit, or tendency to respond. In the case of operant research, however, probability of behavior is studied for its own sake, rather than for its implications for such intervening conceptual entities.

In addition, the application of operant procedures to children places great emphasis on the behavior of individuals rather than on average or group results. For example, different procedures may be necessary in order to bring about a common behavioral change in all children because of our inability to control the heredity and past histories of our subjects. As a consequence of this, great emphasis must be placed on experimental control rather than relying on statistical adjustments to smooth out irregularities.

This approach lends itself to the discovery and isolation of new manipulable variables, e.g., new reinforcers, deprivation regimes, and training procedures. It is quite different from the approaches which entail observing behavioral changes that occur under so-called "natural" conditions or which entail sampling repertoires of behavior at different points in time. These are oriented more toward the establishment of norms. The present approach also differs in part from those which employ groups of children in a laboratory context to test deductions derived from the postulates of a formalized system of behavior. Here the interest seems to lie more in the system than in the child.

Operant Procedures with Children

During the past three years, my colleagues and I have observed the behavior of several hundred children in an experimental situation which makes use of operant procedures. Many of the characteristics of the situation are arbitrary and may be altered



FIG. 1. Subject at the experimental console.

without too much difficulty. As was suggested earlier, however, one characteristic is basic to this as well as to all operant conditioning situations. This is the child's operating on his environment to produce stimulus changes which feed back to him and alter his probability of responding.

In the case of our specific procedures, a child sits at a console in a relatively isolated experimental cubicle (Fig. 1). Before him are a manipulandum (an enclosed telegraph key), colored lights

used as discriminative stimuli, a translucent screen on which pictures or other stimuli are projected, and a tray into which reinforcers are delivered. All of these are on the face of the console. Inside is a Gerbrands universal feeder for delivering reinforcers, an automatic projector, a buzzer, and additional lights.

The telegraph key is attached to a recording apparatus in an adjoining room. Each time the child presses the key, his response is indicated by a moving pen on a continuous sheet of paper. This produces a series of records like those shown in Figs. 2 through 7. Every response advances the pen upward on the cumulative recorder a small but constant amount. After a certain number of responses, the pen is reset and a new excursion is begun.* The paper on which the responses are recorded is pulled to the left at a constant rate. Thus, changes in rate of responding may be studied by examining the changes in slope of the cumulative records: a steep slope indicates a high rate of responding; a less steep slope means a lower rate of responding; a horizontal line shows no responding (pausing). The small diagonal "blips" indicate the occurrence of reinforcement.

The usual procedure at the beginning of training is to bring a child into an experimental cubicle, seat him, show him the manipulandum, and tell him to operate it. Ordinarily, the circuitry is arranged so that the first operation will result in reinforcement. Thus, a trinket or penny is delivered, a loud buzzer sounds, and the yellow or green light projected on the translucent screen is changed to a red one. The red light remains on and the buzzer continues to sound for approximately two seconds. At the end of this time, the buzzer and red light are terminated and the yellow or green light is returned. The child is then instructed to operate the manipulandum again.

Because we are interested in schedules of intermittent reinforcement (i.e., experimental conditions so arranged that responses are not always followed by reinforcement), this time no reinforcing event is allowed to occur. The child is then told that sometimes when he operates the manipulandum he will get a

* The incomplete vertical lines at the tops of the preceding excursions and at the bottoms of those excursions are continuous; they do not appear so, however, because the excursions have been collapsed along the abscissa.

prize and sometimes he will not, and that in order to get a prize he must operate the manipulandum. The experimenter then states that he is going to leave the room for a short time and that the child can win more prizes during this time; the experimenter then leaves the room and closes but does not lock the door. During subsequent sessions such instructions are unnecessary, and the child usually goes directly to his cubicle, closes the door, and starts working.

Trinkets, pennies, and projected 35-mm. Kodachrome transparencies have been used as reinforcers. The trinkets are small plastic and metal objects, e.g., dogs, footballs, rings, clothespins, etc. While trinkets alone are usually adequate for preschool children, they are not for older children, and pennies must frequently be substituted. Sometimes combinations of pennies and trinkets are employed if a child manifests an interest in both.

As was suggested previously, an interesting way to vary response-contingent consequences and thus to produce changes in probability or rate of responding on the manipulandum is to use different schedules of reinforcement. No detailed description of the large number of possible schedules will be attempted here. If such information is desired it may be obtained from the volume by Ferster and Skinner (6). A few examples of simple but interesting ones are the fixed ratio (FR), the fixed interval (FI), and the variable interval (VI). In the case of the FR, every N th response is reinforced; i.e., a certain number of responses must be made before a response is reinforced. FI schedules place a time rather than a behavioral restriction on reinforcement; thus, with the FI schedule a certain fixed amount of time must elapse after the previous reinforcement before a response is again reinforced. The VI schedule is similar to this except that varying rather than fixed intervals must elapse. These schedules in altering response probability produce different frequencies of responding over time, i.e., different rate patterns of responding. The patterns may be recorded and studied as each response advances the pen on a cumulative recorder a small but constant distance. When these procedures are used with lower animals (in conjunction with such homeostatic reinforcers as food or water), fixed ratios usually produce high constant rates of responding, fixed intervals pro-

duce acceleratory patterns (i.e., pauses after reinforcement followed by gradual accelerations in rate of responding), and variable intervals produce relatively constant rates but rates which are lower than those produced by fixed ratios.

Examples of Behavior with Different Reinforcement Conditions

In Fig. 2 are depicted the first-session records of two children on small FR schedules. In the record of subject A, 14 reinforce-

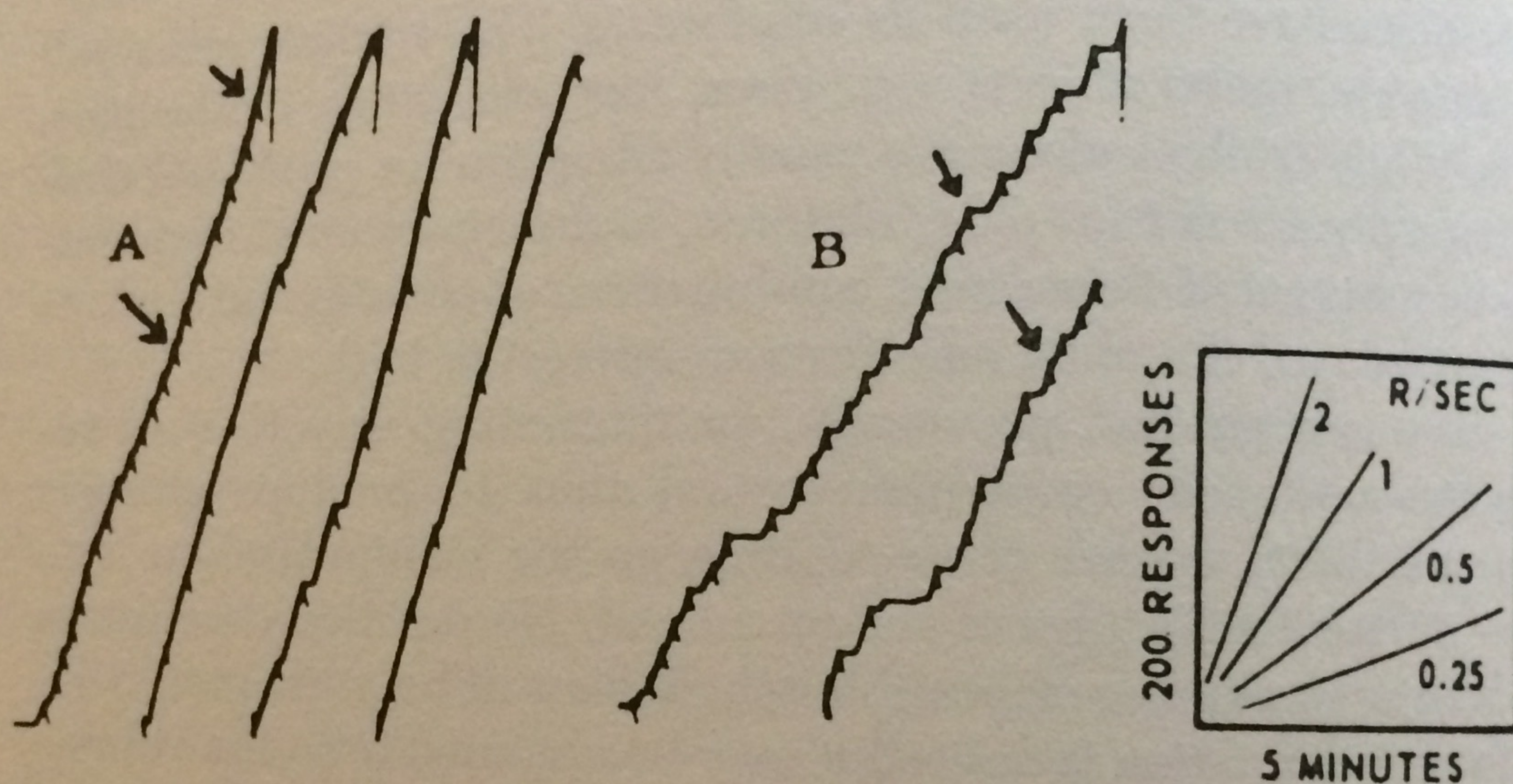


FIG. 2. First-session FR records. The first subject (A) was begun on FR 15, changed to FR 25, and later shifted to FR 45. A high regular rate of responding was developed. The second subject (B) was also begun on FR 15 and shifted to FR 25; he was later dropped back to FR 15, however, because of his irregular performance.

ments were given at FR 15 (i.e., one reinforcement after each 15 responses). At that point the ratio was changed to 25, at which value six reinforcements were given; it was then further increased to FR 45. The schedule was kept at this value for the remainder of the session. For this subject, rate of responding was high, and it became more and more regular. This record indicates that the schedule came to exercise considerable influence or control over performance, and that probability of response is high and constant with such a schedule.

Subject B was first given 19 reinforcements at FR 15, then shifted to FR 25. After 13 reinforcements at this value, the ratio

was dropped back to 15 because of increased pausing and decreasing rates of responding. A comparison of this record with the previous one suggests that the same procedures cannot be used with all subjects. Subject *B* undoubtedly could have been brought successfully to FR 45 if the increase had been more gradual. Averaging the records of these two subjects would have revealed nothing. The fourth excursion of subject *A* was already highly regular. Moreover, averaging would have concealed the necessity for differential treatment of different subjects.

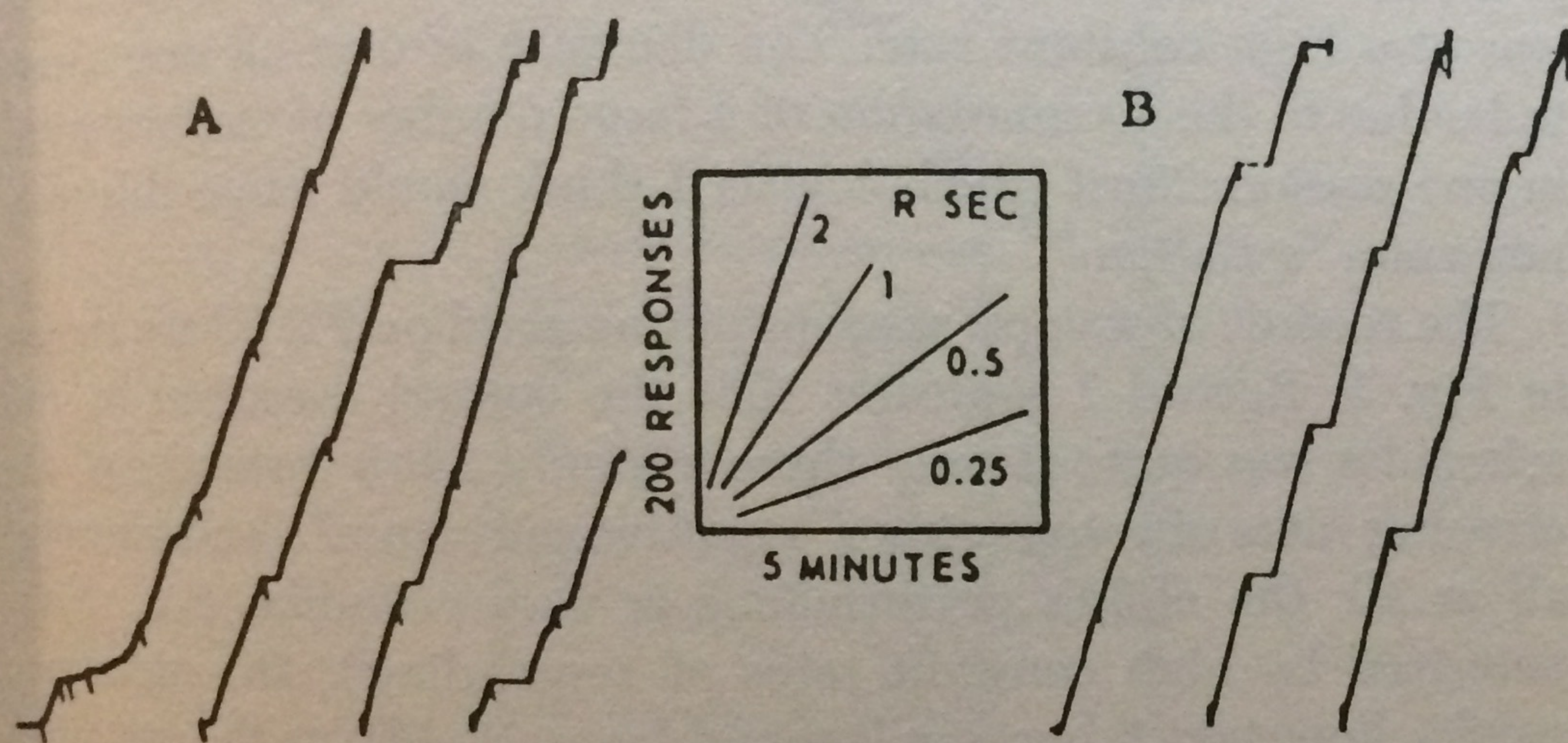


FIG. 3. First-session FI records. The subject (*A*) was given five reinforcements on a VI .5 before being shifted to FI 1. The second subject (*B*) was begun and maintained on an FI 1.

Figure 3 presents the first-session records of two subjects on fixed intervals of one minute (FI 1). Subject *A* was given five reinforcements on a variable interval of one-half minute (VI .5) before being shifted to the FI 1. Subject *B* was begun and maintained on an FI 1. In spite of their dissimilarities, both subjects soon began to pause after reinforcement and then to accelerate abruptly to a terminal rate. Both of these records perhaps depict the occurrence of learning. In any event, the schedule quickly gained control over behavior to the extent of producing new rate patterns and thus altered probabilities of response. The records also show how rapidly the behavior of these children is changed, illustrating once again that the child is a very sensitive organism, and that environmental changes (in this case the re-

inforcing contingencies) are very quickly reflected in the child's behavior.

Let us turn our attention to the concept of motivation. One might view operant procedures as acceptable for studying the influence of schedules yet raise questions as to sensitivity of the technique to motivational manipulations. In Fig. 4 are depicted the first-session records of two children on small fixed ratios: subject A was on FR 10, subject B was on FR 15. Both showed deceleration of over-all rate throughout the session. This deceleration was produced by increased pausing, but when each child responded it was at a high constant rate. The decrease in over-all rate seems to be due to the accumulation of a large number of trinkets within one session. Most psychologists I think would name this phenomenon "satiation."

The records of several sessions of one child on FR 60 are shown in Fig. 5. Record 1 indicates that the control exercised by the schedules was quite strong—there are only a few instances of decreasing rates of responding ("negative curvature") and pausing; all in all, the child's performance is very ratio-like (i.e., characterized by high constant rates of responding). On successive weeks, however, it became less and less ratio-like as the instances of curvature and intermediate rates increased (Record 2). After a number of sessions, different trinkets were employed. The effect of this change is seen in Record 3: the rate has increased, most instances of curvature and intermediate rates have disappeared, and in general the performance has become again more ratio-like. Depicted in these records are the effects of reduced and then increased reinforcement. A comparison of Fig. 4 with Fig. 5 makes evident the differences in the effect of reduced reinforcement and the effect of a schedule producing what we called satiation. Satiation produced by a too rapid accumulation of trinkets was characterized by increased pausing but high constant rates of responding, whereas the effect produced by reduced reinforcement was characterized not only by increased pausing, but also by increased instances of curvature and intermediate rates of responding as well.

These records suggest that operant behavior maintained by intermittent schedules is very sensitive to manipulations of moti-

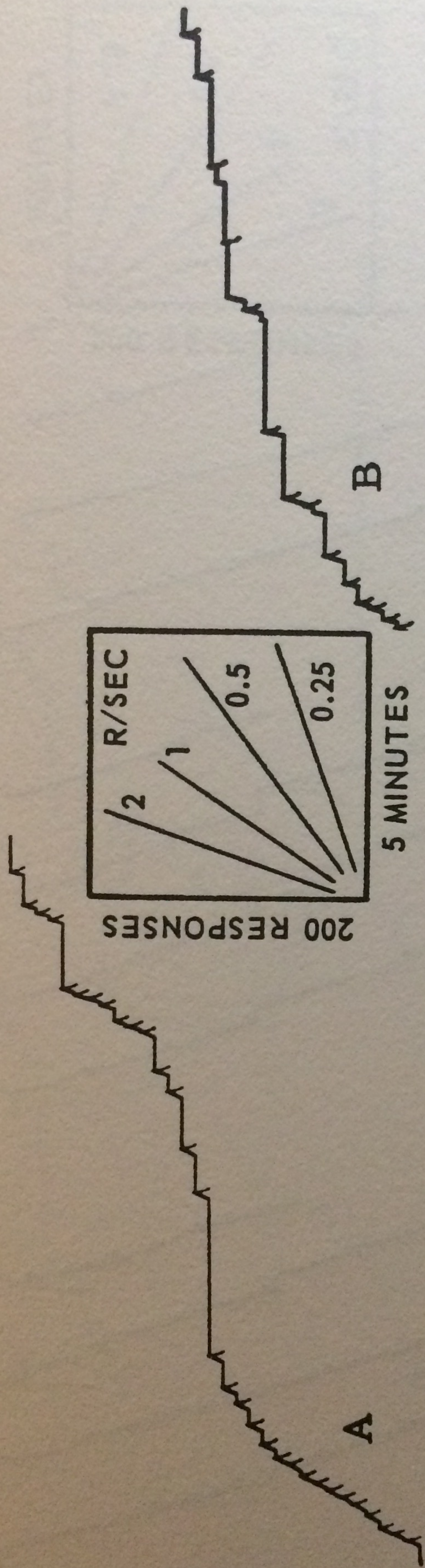


FIG. 4. Over-all rate changes with small FR's. The first subject (A) is on FR 10; the second (B) is on FR 15.

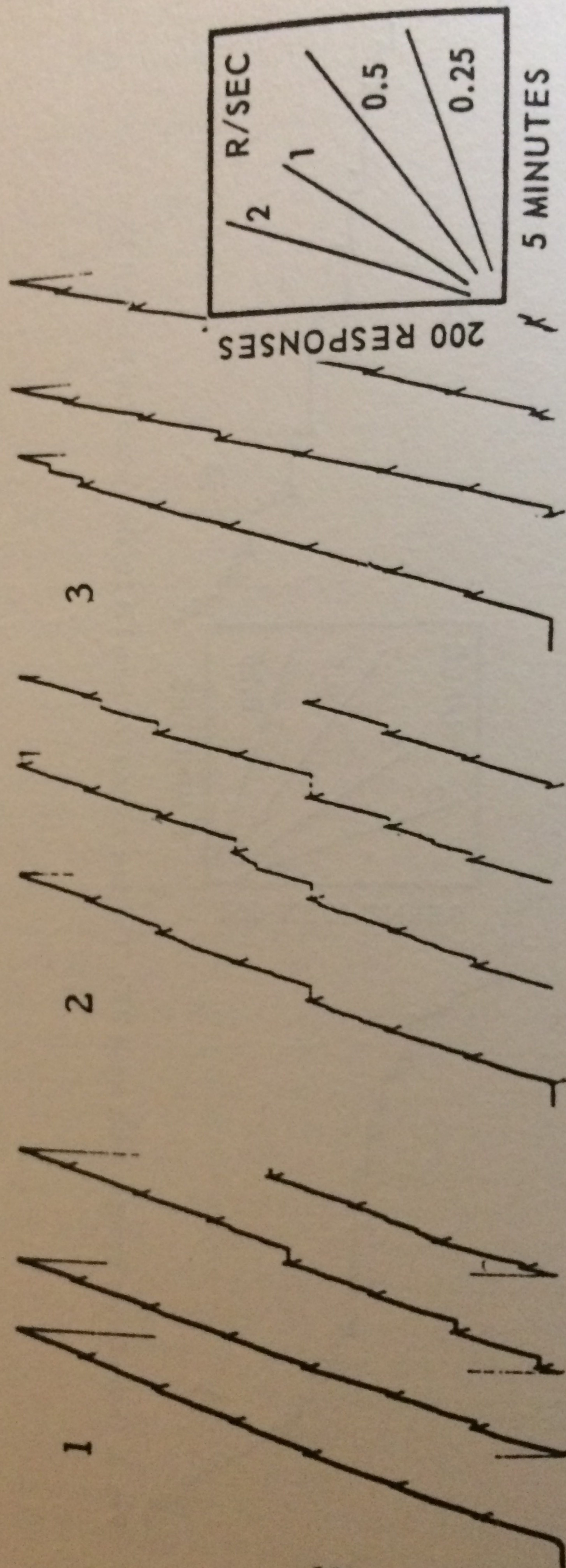


FIG. 5. Changes in FR rate patterns produced by variation in reinforcement. Record 1 shows the fifth session of a subject on FR 60; record 2 shows the same subject's tenth session; record 3 is the record of his eleventh session at which time different trinkets were employed.

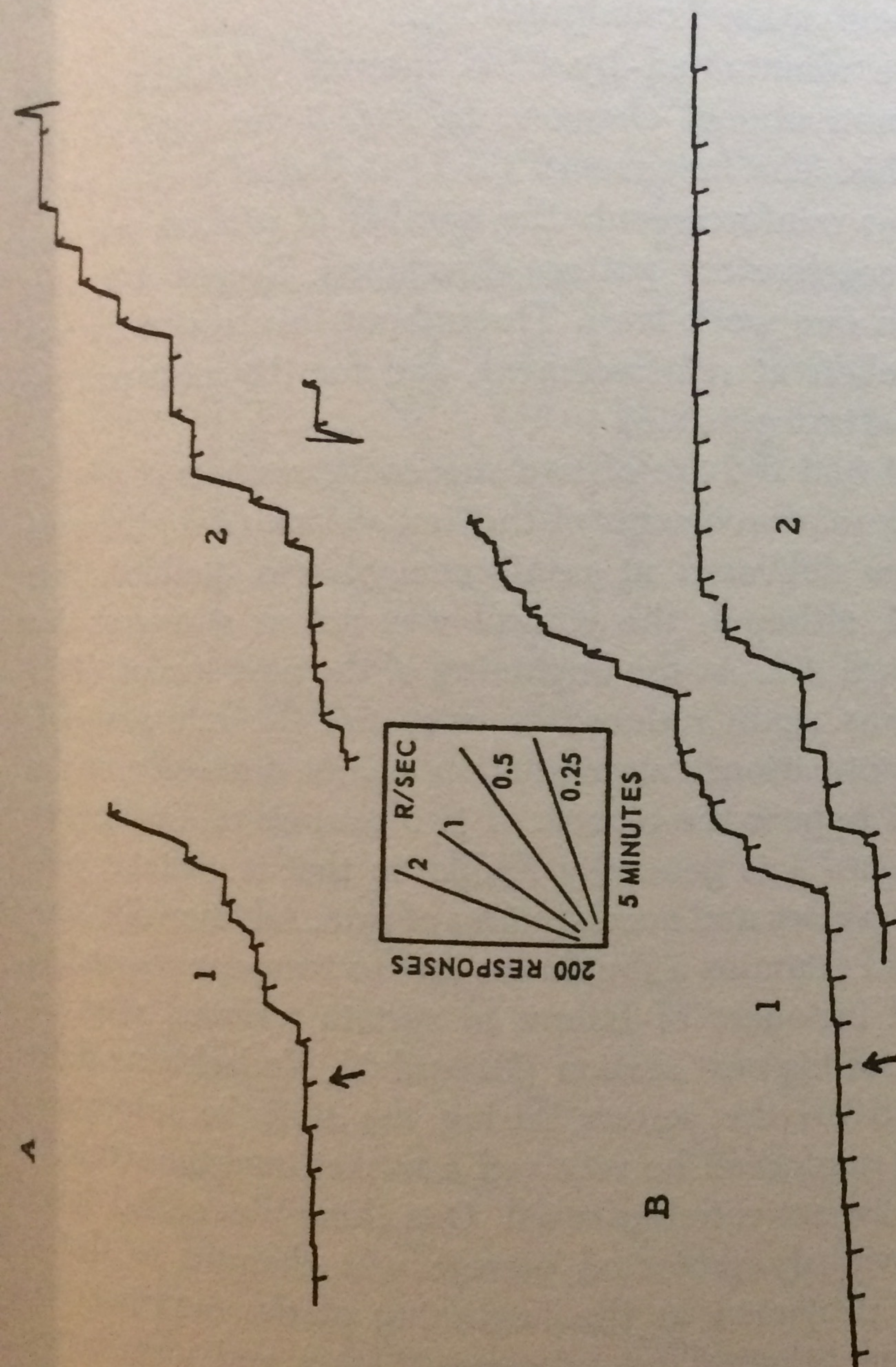


FIG. 6. The effect on FI's of increasing and decreasing reinforcement. Record A-1 shows a subject on FI 1 being reinforced with trinkets. The arrow indicates the point where the number of trinkets given at reinforcement was increased from one to two; this procedure was continued throughout the subject's next session (Record A-2). Record B-1 is the record of a subject on FI 1 being reinforced with pennies. The arrow shows where the number of pennies was increased from one to two; this number was reduced to one, however, at the beginning of the next session (Record B-2).

vational variables. In the present case the effects of the two motivational operations were reflected differentially. It is doubtful indeed that behavior in a maze or in a similar experimental situation would be sensitive enough to reflect differentially the effects of these two motivational manipulations.

Performance maintained by fixed interval schedules is also sensitive to motivational changes. In Fig. 6 are depicted two instances of this. The first record (A-1) is that of a child on an FI 1; after four reinforcements the number of trinkets was doubled and an acceleratory pattern developed. Record A-2 is for the same child one week later. Throughout this session she was given two trinkets at reinforcement, and for the most part the acceleratory pattern persisted.

Records B-1 and B-2 are of two successive sessions of another child. After six reinforcements of the first session (B-1) the number of pennies delivered at reinforcement was doubled. Rate was increased, although the control was not as strong as that shown in Record A-2. At the beginning of the next session (B-2) the number was again reduced to one, and the rate soon fell.

One final motivational manipulation merits discussion at this time. In Fig. 7 appear the records of two sessions of a subject on an FI 1.5. Record 1 is generally FI-like in that it contains post-reinforcement pauses and accelerations of rate. Additionally, however, the record contains a roughness due to irregular responding ("grain") and instances of failure to sustain terminal rates. At the beginning of his next session (Record 2), Kodachrome slides were projected on the screen during the time he responded. When he was reinforced he received a trinket, and the red light and buzzer were activated as usual. One thing was added, however: the previously projected picture was changed so that a new one was projected at the beginning of the next interval. Notice that the terminal rates became higher and were better sustained. Records of control experiments which entailed projecting pictures only during reinforcement did not show this effect. When subjects were interrogated in regard to the procedure, they reported that they liked the pictures at first but then became tired of them, and in fact worked to get rid of them. This finding is of interest in its own right, but it may also have im-

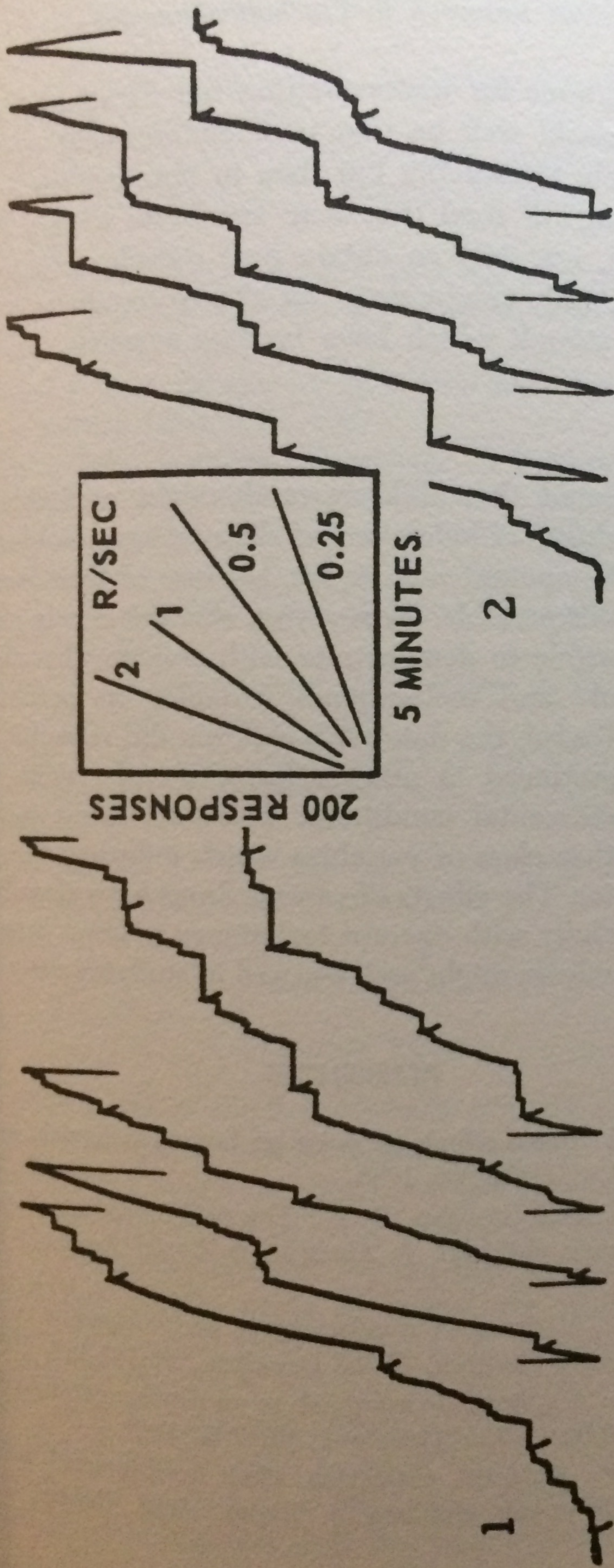


FIG. 7. The effect of adding projected pictures. Record 1 is the record of a subject on FI 1.5 reinforced with both pennies and trinkets. Projected pictures which changed at reinforcement were added to the existing reinforcements regimes at the beginning of the next session (Record 2).

portant implications for understanding the FI schedules in all organisms. It could well be that post-reinforcement stimuli are at first positively reinforcing but then in time become aversive. The rat working for food thus may accelerate toward the end of the interval, not only to obtain new stimulus consequences which are positively reinforcing, but also to terminate old post-reinforcement stimuli which have become aversive.

Summary

I have indicated that child research might profitably entail studying probability of behavior and discovering variables which influence it. The operant techniques, because of their great sensitivity, make this possible. By studying changes in rate patterns, it has been possible to demonstrate with children the effects of various schedule and motivational variables on performance. Although less lawful, the data with children did resemble rather closely those produced in other organisms under more rigidly controlled experimental conditions. Basically, drugs might be viewed as another class of variables which influence the probability of behavior. The effects of various drugs have already been studied successfully with operant techniques in lower organisms. The same procedures might well be used in studying drug effects in children.

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DISCUSSION

SEYMOUR FISHER

Dr. Long is one of the few research workers currently exploring the use of operant conditioning techniques in the study of child behavior. I might say that I feel the approach is a particularly provocative one, not only for its potential promise in a wide variety of situations, but also for the basic concepts underlying its application. As Dr. Long has noted, the growth of operant techniques in the past 20 years has been remarkable: originally introduced in the study of learning in lower organisms, the Method (as it is sometimes referred to by its ardent followers) has recently been extended to adult humans, both normal and psychotic. Now we have some indications of its use with children. Although Dr. Long has, thus far, been content to omit drugs

as independent variables in his own research, the implications of this method for drug research are numerous. Drug effects on learning, concept formation, perception, social relationships, and interactions with reward-punishment schedules could all conceivably be investigated within this sort of framework. I would very much like to see such studies come about.

I am especially impressed with the stability of the behavioral measurements that can be obtained with these techniques. One of the most persistent problems in doing drug research with children is the variability of the behavior being studied. Most experimental designs require pre- and postdrug measurement, and the investigator is often swamped by "spontaneous" factors which make his test measurements unreliable. Neat, repeatable measures of behavior are difficult to find. From the data presented by Dr. Long, it appears that some operant schedules produce highly stable behavior, and thus offer a distinct advantage for reliably assessing the effects of drug intervention.

Stability, however, is not necessarily the same thing as sensitivity. Dr. Long has dramatically illustrated that the child's behavior may be quite sensitive to changes in both schedules and quality of reinforcement. Nevertheless, one must consider the possibility that these response patterns may not be especially sensitive to other variables, e.g., drugs. As the behavior patterns become more and more stable, they may lose their sensitivity to significant factors—just as any highly overlearned response becomes resistant to modification.

For the clinician who may raise a question about the meaningfulness of these behavioral measures, I might simply mention two points. First, as we gather more information about drug effects on behavior in general, we should be in a better position to use these drugs most effectively in the clinical situation. Second, I suspect that eventually it will be necessary to correlate findings from drug effects in an operant conditioning situation with effects demonstrated in the real-life, hospital, school, or home situation.

One final note of caution might be added. Arm-in-arm with Dr. Long, I should like to emphasize the objectivity and ease of quantification in the operant situation. We badly need these virtues in our research. I hope that the complex terminology

and instrumentation will not frighten off any interested research workers. At the same time, I become somewhat leery when I hear of a situation in which the child is brought into an experimental room, the door closed, and a segment of his behavior subsequently observed via automatic recording devices. I am reminded of a recent report by Lepley (1), who was studying the rat in an operant conditioning experiment:

When an assistant to the assistant got around to harvesting a six weeks' production of data from a Skinner-box, the crop yield, as represented by the automatic recording device, was remarkable for the latter part of the period. He opened up the box and discovered that Mrs. Rat was rearing a family and that the offspring were running the machinery! (1, p. 298.)

Let us not lose sight of the child.

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DISCUSSION

JACOB L. GEWIRTZ

The method of the conditioning of the free operant with that of the highly regular base line to which the effects of treatments can be referred within an individual subject, together can provide a most powerful method of behavior analysis. This method makes possible, even in such complex organisms as the human adult and child, the efficient examination of the effects of many different types of important experimental variables, ranging from those involved in the development of social behavior and personality to psychopharmacological agents. These methods originally were brought together creatively and popularized in psychological research by Skinner (14, 15), and in recent years some of his associates and others (1, 4, 5, 16) have written about the methods and have employed them. I have elsewhere written in some detail about the possibilities of the method for use in child research, and particularly for the intensive investigation of the etiology and the behavior characteristics of emotional dependence and related social behaviors (6).

Very similar methods have been employed to good effect in

fields other than behavioral psychology. Thus, for example, a steady rate of pulse, respiration, or EEG (e.g., alpha rhythm) is elicited under a given set of conditions, and the effect of some treatment (or level of treatment) to which the organism is subjected is then reflected in systematic changes in this regular output rate. Use of the "lie detector," in which changes from base lines in autonomic response rates are correlated with classes of questions asked of the subject, represents an example of the base line method in common use. So, too, the effects of a variety of experimental treatments (including drugs) might well be reflected in reliable behavior outputs of the sort that Dr. Long has described. The possibly subtle effects of drug treatments, for example, may well be amplified in base lines of voluntary responses.

To supplement Dr. Long's presentation, I shall attempt in this discussion to outline some of the essential characteristics of the base line method of behavioral analysis as employed in a setting involving the free operant conditioning of voluntary responses in children. In this way, with Dr. Long's most useful examples fresh in mind to guide us, the issues involved in use of the method should be highlighted effectively. But first, let us consider the nature of the free operant.

When the experimenter establishes a controlled setting to represent his abstraction of the essential elements of a set of uncontrolled conditions he wishes to study, he may look for the effects of his independent variables in behavior emitted under either of (at least) two different types of conditions: he may focus on a *restricted* response setting involving behavior "trials." That is, he creates an occasion, the trial, during which the subject is free to exhibit a behavior or behavior sequence, at the end of which he is not given the opportunity to repeat the response until the next trial, as defined by the experimenter. Thus, to obtain food, the subject may traverse a long, straight runway, turn right or left at the choice point in the T-maze on his way to an end box, or make a sequence of choice responses as in a serial maze. Alternatively, the experimenter may focus on *free* behavior, the free operant case where the occasions for behavior

emission are not separated by trials as defined above. In this case, after emitting a response of rather short duration, the subject is in the same place prepared again to respond, if he is so inclined. Thus, the dependent variables in the free operant case would be based on the frequency of a given response in time, i.e., response rate.

The major advantage of the free operant in research is that there are, generally, no restrictions when it is used on the frequency or rate with which a given response can occur, as there would be in the case of behavior restricted by trials. Thus, the assessment of changes in response rate from moment to moment becomes possible, and the experimenter gains considerable flexibility, for he is free to define the response employed to suit his own research ends.

Dr. Long has presented a most effective illustration of the method of free operant conditioning as he has employed it in the study of an important class of child behavior. The behavior output curves he has obtained from young children are impressive for their orderliness when we consider that he is in an early stage of research on the voluntary behavior of a class of subjects about whose behavior dispositions in such conditioning settings we know relatively little as yet.

Moreover, for those interested in the reinforcing effectiveness (both unconditioned and conditioned) of a variety of stimuli commonly present in the typical environment of children, Dr. Long's paper represents a useful, substantive contribution. And he seems to be following up in a fruitful way some of the interesting leads in his data, providing a timely illustration of his contention that emphasis on the experimental control rather than on the statistical control of variables could readily lead to the uncovering of new independent variables. Thus, there is the provocative indication in his data that some post-reinforcing stimuli which appeared initially to be positive reinforcers for his child subjects may actually have become aversive after the subjects seemed to have become satiated for them.

In this connection, it is intriguing to speculate about a possibility that Dr. Long has advanced: that the operant behavior

of his subjects may be rather sensitive to manipulations of motivational variables. He illustrated this point with the finding that his subjects appeared to become satiated for trinkets as reinforcing stimuli; i.e., their rate of response for trinkets decreased regularly during the session as a positive function of the number of trinkets they had received.

Unlike Dr. Long's subjects who became satiated rather quickly, animal subjects responding for the conventional reinforcers of food or water in operant learning settings almost never satiate during an experimental session. This is because the experimenter fairly well understands how to apply the deprivation-satiation laws for food and water to his subject, and hence can keep that subject on an effective deprivation schedule while he dispenses the reinforcer in relatively small amounts. He does this because typically he is interested not in deprivation-satiation relationships, but rather in other problems which he can study by manipulating reinforcing stimuli to his advantage.

However, as Dr. Long is one of few persons currently working on these problems, and has but little lore to rely upon, he has been attempting simply to discover reinforcing stimuli which would function to condition children's operant behavior. In pursuing this purpose, he seems to be discovering some most interesting facts. These facts will constitute the lore which researchers who follow Dr. Long will be able to fall back upon in their operant conditioning research with children.

Thus, Dr. Long's finding which suggests that the child may be satiable for the trinket (as a reinforcing stimulus) brings to mind the possibility that the effectiveness of trinkets as reinforcing stimuli might be increased following some period of time during which the subject is limited from access to them; i.e., that the reinforcing effectiveness of trinkets might be sensitive also to a deprivation (of trinkets) operation. If this were so, as seems likely, then a reinforcer which does not appear biologically necessary (in the same sense that food is necessary) would be responsive to deprivation and satiation operations of a similar order as those controlling the reinforcers of those drive systems commonly labeled primary appetitive.

Another most interesting question for us to ponder is: what is the "source" of the reinforcing value of the trinket? It is likely that its value as a reinforcer is, for the most part, conditioned; i.e., that it developed reinforcer value for the typical child because it was paired with (or stood as discriminative for) a variety of functioning reinforcers for him. In addition, if the effectiveness of the trinket as a reinforcing stimulus is under the control of deprivation-satiation conditions, we would have another instance (7, 8) in which a presumably conditioned reinforcing stimulus is sensitive to conditions of deprivation and satiation similarly as are the reinforcers of the primary appetitive drives.

In this connection also, it is important to note that the recent papers of a number of researchers in the field of animal behavior and learning (2, 3, 9, 11, 12, 13) suggest a most intriguing possibility: that a large variety of environmental stimuli (novel stimuli or simply environmental changes—e.g., sounds, lights, etc., opportunities to manipulate, to explore, or to observe) may function as reinforcers of instrumental behavior when made contingent upon it. It is important to note that such stimuli do not appear biologically necessary, as would be food, nor do they appear to have attained their reinforcing value through conditioning. It would seem important to take account of this possibility when considering how it is that such stimuli as trinkets, for example, have reinforcing value, and when employing discriminative stimuli in operant conditioning settings generally. Of equal importance is the possibility, suggested by the analysis of habituation by such investigators as Hinde (10) and Verplanck (17), that the effectiveness of many (but not necessarily all) such reinforcing stimuli for an organism may be under the control of deprivation-satiation operations which determine the rate at which a stimulus is presented to the subject in the period immediately preceding a test (whether or not those stimuli are made contingent upon the subject's behavior). Indeed, on this basis, the possibility exists that food and water may be the exceptional rather than the typical stimuli, in the sense that for them there would be apparent physical constraints (e.g., the size of the stomach) which would control their intake for an

organism, and hence their reinforcing qualities. For the more typical stimuli under deprivation-satiation control, the limits of deprivation and satiation must yet be determined.

But now, what of Dr. Fisher's question about the "meaning" of simple free operant behaviors? This is not a difficult question to answer, if what he has in mind by the term "meaning" is the *manifest* or *face* validity of the behavior; for this is an issue which enters in all experimental research on behavior—particularly when we would attempt to systematically manipulate events in an experimental setting which is established to represent in abstracted form the essentials of a set of naturally occurring, uncontrolled conditions to which we intend ultimately to generalize our findings.

Thus, an analysis of the motor elements of behaviors would not denote or restrict their manifest meaning for most of the purposes of research in complex social processes, just as the motor elements of, say, walking would not be adequately descriptive of the response sequence for the end of escaping the police, of purchasing a gift, or of rushing to meet a loved one. It is the context of the behavior sequence which gives it its manifest meaning. The circumstances which are directly contingent upon what otherwise would be the trivial response of a marble being dropped into a hole, or a word being emitted, or a telegraph key being pressed (i.e., the reinforcing condition or "goal" maintaining the response) can be most important for a subject. A child may press a key to bring on the appearance of his mother (which is equally as reasonable as pressing a key to bring on the appearance of a trinket), and a rather stable output of behavior might be emitted for that reinforcing event in a standard setting.

In addition to its meaning in the sense of *reliability* or *replicability*, the behavior of our example would, in a logical sense, have exactly the same manifest meaning as would, say, the spontaneous behavior of a child searching for his mother. It would also have very much the same manifest meaning as would the behavior of a child who, on signal, could choose to go (a) to his mother, (b) to some other familiar adult, (c) to some object, or (d) not to respond at all, and chose in this context to go to his mother.

It was in research contexts much like these that the concept of *reinforcing stimulus* was developed to order the class of stimulus event which, when made to follow directly a given response, systematically affects the rate or some other aspect of the response. Many of the stimulus events which afford such control over responses are supplied by people (e.g., approval, affection), hence *social* behavior or behavior for *social* reinforcers.

In the final analysis, of course, the meaning of any behavior in the sense of its *validity* would be entirely dependent upon two factors: first, the functional relationships into which it enters, particularly with independent variables, but with other classes of behavior variables, as well; and second, how reasonable those relationships appear when referred to some theory of the researcher, however informal or preliminary.

Indeed, in this context we must always be open to the possibility that the dependable, regular rate of output (under some standard condition) of what originally appeared to be some trivial and insignificant behavior might prove to be most sensitive to some important experimental treatment variables. Of course, in this event the behavior earlier thought trivial would be seen in the new light, as representing some class of behavior affected by the treatment which had been predicted earlier; and it would no longer be trivial in the sense that it was unrelated to important variables in either the formal or informal theory of the researcher.

Let me now draw more precisely a most important conclusion: standard conditions can be established in operant conditioning settings to parallel almost every problem or method of behavioral psychology listed by Dr. McCandless and by Dr. Layman. A large variety of social and nonsocial conditions could be readily articulated into operant conditioning settings; if successfully implemented, they would give the researcher a high degree of meaningful control over those conditions, usually making him many times more efficient than he would be studying such phenomena as they occur in natural (i.e., uncontrolled) settings, or even under the controls employed in some of the experimental cases that Dr. McCandless has listed. The researcher would have a powerful tool of experimental analysis which would allow him

to focus directly and systematically on the fine grain of the conditions which can exert control over the important human behavior systems. The scientist may study such conditions in themselves (e.g., the reinforcing effectiveness of a variety of potential reinforcing stimuli), as Dr. Long has done; or he may reflect the effects of independent treatment variables he wishes to investigate in the reliable dependent variables which a standard set of those conditions can generate.

The important consideration for both these experimental cases, which employ the methods of operant conditioning and the highly orderly individual base line, is that they make it possible for the behavior scientist to exercise considerable control over a variety of behaviors in important, naturally occurring settings. Thus, to illustrate the second experimental case, many important conditions might be articulated into operant conditioning situations as reinforcing stimuli, and the rate of a subject's response for presentations of those stimuli would indicate their relative importance for him. This might be done for the purpose of charting the behavior patterns characteristic of the child (i.e., for diagnosis), or of relating those patterns to other behavior patterns, or to antecedents in the life of the child. In this way, for example, one could study the conditions under which social stimuli provided by the behaviors (e.g., attention or approval) of an adult are important (i.e., reinforcing) for a child.

The reinforcing value of many stimuli, in addition to those provided by the behavior of other people, can be determined for a child in this way. The range of stimuli which might function as reinforcers of behavior in operant conditioning would run from photographs or drawings, apparently meaningful or meaningless, to doll-puppet settings in which the first of two previously stationary puppets gives a hug or a kiss to the second, or possibly punches it. Indeed, in addition to this last example, the reinforcing value of a variety of the events which would occur in free doll-play could be studied. Thus, to focus on a relatively pure hostile response, the reinforcing stimulus might be a hammer or weight falling on a doll. Or the reinforcing event might be provided for the child by the opening of a cabinet which gives him

the opportunity to hug, or inflict damage to, a doll. Indeed, the reinforcing value for a child of a variety of such happenings might be studied serially. Essentially, this would constitute a *projective* test which would yield a wide range of behavior scores for children (or one child on different occasions), and assessments of the relative value of reinforcing events which could be replicated readily.

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COMPARATIVE DRUG-BEHAVIOR ANALYSIS

SHERMAN ROSS

I WOULD LIKE to state at the outset some of the assumptions which I am willing to make and which I hope you are willing to grant:

1. Children are here to stay for a while, even in increasing numbers.

2. The research efforts to date in the area of drug effects on children represent the same problems and difficulties as other studies of drug effects.

3. Unraveling the basic problems of development is a long and difficult task which involves many false starts.

4. Scientists will continue to do the kind of research studies that they care to do by the techniques they are trained to do.

5. Changes in research habits and research concepts come slowly.

6. There will continue to be many difficulties and confusion in interdisciplinary and nondisciplined group attempts at unraveling some of these fundamental problems.

At conferences it often happens that distinguished people representing a variety of disciplines are brought together to consider a common problem. In such meetings I would like to plead for each discipline to go its own way in its attempts to unravel many of the complicated problems.

Comparative Psychology

I want to turn to some of the problems of comparative psychology. These are immensely meaningful times to reconsider these particular problems. The Darwin centennial is in 1959. Within the past two years has been the 100th anniversary of the birth of Freud. The year 1856 marked the first time a laboratory

rat was used as an operative preparation with adrenal removal. My deduction from all of this is that 100 years ago must have been a wonderful time.

In the next immediate few years we will be re-examining some of the very fundamental concepts that have come out of evolutionary theory, particularly regarding behavior. Many psychologists are immensely naive about the core of this problem. It takes a distinguished and experienced psychologist to put us straight. Neal Miller, for example, in an address he gave recently, defined the relationship between rat and human behavior. His approach is clever and I think correct. He says that we can find counterparts in human behavior of almost everything that we can measure and find in rat behavior, but not the opposite. It is a very important kind of statement and permits an analysis of some of the comparative problems.

The major theme that I bring before you is that what a comparative science deals with is similarities (which are what everybody is looking for) and with differences. How easily we undersell ourselves by the heavy investment in overt similarities and complete neglect of differences. The property of a comparative science is that it is concerned with both differences and similarities (7). It is perhaps because of some analyses of differences that we have not really developed a comparative psychology. Many times I argue that we should not develop such a science. For example, I have been told that one of the tranquilizers, a major substance of frequent use in the veterinary field, is particularly useful in quieting dogs, cows, and pigs, but doesn't work on horses. It agitates horses. The phenomenon of interspecies differences is very acceptable to anyone who understands biological phenomena.

In our desperate need to draw the great generalizations that will cover not only human behavior, but all behavior of any living organism—plant and animal—and of existing and prehistoric ones, many of us sometimes overlook the problem of differences. It takes other sensitive individuals to point these out to us. I am trying now to indicate that a search is going on from a comparative point of view and that the principle which Neal Miller stated very clearly is being recognized.

Comparative analyses of behavior in fields other than psychology are doomed, I am afraid, to be at best background sciences. In the training program of the physician, the novice is indeed uninterested in the problems of comparative anatomy, comparative neurology, comparative physiology. He is interested in one particular organism, the human organism, and that is what he wants to know about. But in the area of psychology, we have in the past 25 or 30 years invested so much in the analysis of the rat's behavior that the investment has been productive for the analysis of human behavior.

In this connection, I would like to tell you a little story, the point of which I believe in very much. It was told to me about Professor Robert Yerkes. When graduate students at Yale were required to defend their theses publicly before an audience of their professors, their fellow students, and others who were interested, Professor Yerkes would almost always ask (if the study happened to involve animals), "What is the relevance of your work to human behavior?" Since the question could be anticipated, the students quickly learned that the acceptable reply included statements about phylogenetic continuity, evolutionary development, process similarity, etc. The final point in the response was: "Even if none of the foregoing reasons is particularly appropriate, it is indeed important to study the rat (or the monkey or the cat) for its own sake as a co-existent species on the face of the planet, and we ought to know about these things." Such a reply is perfectly reasonable, and all of us might agree with such a notion. This method of dealing with the question of human relevance went very well until a group of students, during Professor Yerkes' absence, decided to question a young lady who was defending a research study of children. When the moment came for questions from the floor, the students asked, "What is the relevance of your research to rat behavior?" The young lady was well prepared. With a serious face, she very straightforwardly made the usual response about phylogenetic continuity, evolutionary development, etc. As her final point, she said, "Even if none of these things is true, it is important to study the human child for its own sake." That is the statement I agree with.

I am not here to plead the argument of the study of the human child. Many of the participants here represent that kind of interest from different points of view. The special social climate which called this conference forward is the impact of certain classes and kinds of drugs—we don't even know how to classify them exactly—and the effects of such drug treatment on human children. I want to define this as the central theme of how we go about trying to answer questions about drug research with children. I have identified so far a very special concern with human children with which I am willing to agree, and a social and intellectual climate—a public climate, if you will—of interest in drug effects.

Developmental Research

I want to take a rapid look now at what the research contributions, at least from the field of psychology, have been over the recent past. I want to do it rapidly, and do it in the form of broad generalizations which I don't care for but which might be useful and provocative.

The complex processes which we label development have given us a great deal of conceptual trouble over the years. A conference was held at the University of Minnesota in 1955 to recognize some 30 years of work at the Institute of Child Welfare (3). The proceedings of this conference are an excellent representation of the complexities, the presumed importance, and the differential approaches of people representing a variety of disciplines and concerns. One thing is clear, to me at least. The research contributions which have characterized American psychology for the past 30 years have stressed behaviorally the process of learning in the white rat or the human subject, examining this in a quantitative and objective style, the end point of this work being its relevance to human behavior. I do not, and cannot, disagree with this work of the past. I can indicate that the efforts entering into the analysis of developmental processes did decline. This decline was perhaps correlated with the decline in work which we may call comparative in nature. Very few psychologists are rat psychologists in the sense of being interested in the rat per se; I think most of them are interested in the behavior of humans.

Coupled with this characterization of the past quarter of a century, we have also seen other things happening. We have come to see operations almost at a standstill in the area called developmental psychology. These problems have not, as I see it, challenged or attracted the youngsters recently. I think this state of affairs is bad, and I think perhaps we might now be coming to another kind of period.

Another one of the things we have seen is that the psychodynamic point of view is becoming the dominant approach in the analysis of human behavior, in personality analysis, and perhaps even in pediatrics. Here I am referring to the idea that events that happened earlier in time have meaning in analyzing, predicting, or interpreting individual behavior.

Within recent years we have had perhaps a return to the biological basis of psychological behavior, if you will. In the field of comparative psychology, this re-emphasis has come from a number of areas. I want to simply sketch these out, but I will have to omit some of them.

First, we have been captivated by, and many of us have neglected, the work of some of our European colleagues, the ethologists (9, 10), who have reopened in a major way the problem of investigating the nature of innate behavior. They have had a sizable impact, I think, on what psychologists do these days in the research business.

New leads have opened up in the neurophysiological and biochemical fields. I don't think there has been any decline of interest in psychological determinism or in psychodynamic approaches to behavior. I do think, however, that we have had increasing interest in the biological, neurophysiological, and biochemical mechanisms. From this, a new interest is arising in the problems of the analysis of development. It is of more than passing interest to me that Harlow, in his presidential address to the American Psychological Association (2), made a presentation of research on substitute mothers in infant monkey development. Here is a very distinguished and important American psychologist whose work on the effects of cortical ablation has been outstanding. Dr. Eisenberg used the term "learning to learn"; this concept is one of Harlow's major contributions. More recently,

Harlow has been working on the effects of radiation on behavior in monkeys. However, from 25 years of first-line research, the topic which Harlow selected on the occasion of his presidential address was some fascinating work on substitute mothers in the rearing of young monkeys. I think this reflects the kind of contemporary interest to which I am referring.

We have had among the animal psychologists a reopened interest in the problems of the effects of early experience. In most instances they have followed the fundamental psychodynamic hypothesis, and tried to get empirical evidence related to it. We have seen the work from the Roscoe B. Jackson Memorial Laboratory spreading the concept which has been called the "critical period hypothesis" in individual development (8); at this moment, John L. Fuller and his associates are studying the delayed effects of tranquilizing drugs on learning and other aspects of behavior in young dogs during critical periods of development.* From the laboratory at the American Museum of Natural History, we have seen fascinating attempts to manipulate individual development in the rat, essentially by depriving the rat of certain critical kinds of experiences related to maternal behavior.

We have also seen contributions from the mammalian geneticists. I will mention only one in passing. A number of years ago, some of the workers in the area of sound-seizure susceptibility in mice demonstrated a clear developmental function for the incidence of seizures. Starting from day 0 through day 30, a regular increasing incidence of seizures will be found in mice of a specific inbred strain. If studies of this kind are done with enough subjects taken only at those age levels, the developmental function can be plotted. You plot it, you publish it, and there it remains; nobody cares about it. That is the usual fate of a lot of such information until someone becomes interested in the metabolic properties of the convulsing mouse's brain. Then one is able to find a function relating the indirect estimate of the adenosine triphosphate (ATP) concentration in the convulsing mouse's

* This work is being supported by a grant from the National Institute of Mental Health.

brain with age in days. Excitingly, this curve follows the same trends as the incidence-age function.

I think these are mainly suggestive leads. They are, nevertheless, immensely provocative. Such efforts represent some of the directions in which I think we are going.

Experimental psychologists' work with rats has characteristically been limited to short intervals of time. We have therefore very little information that deals with more than a brief span. Such time limitations have come about from the interests of the psychological investigator and from his stress on appropriate controls. And this is precisely the problem that we are worried about and concerned with when we think of drugs and the development of children.

If you look at much of the vast literature, it tends to deal with rats between the ages of roughly 90 and 120 days. That, too, is not accidental. These research habits are built up by the very difficult process of training. One person trains another to do these studies. We learn the hard way that if we use young organisms, 30 or 35 days old, all kinds of variables enter in which are not really needed. We have enough variables to deal with already. So we don't ask or answer questions about developmental factors.

One of the very interesting moves that have come about in the recent past is the springing up of a group of workers who are primarily interested in the effects of early experience (4). A few years ago it was reported that early handling had an effect on the development of stress tolerance in rats. This finding excited a number of workers, and I want to indicate one of the ways in which subsequent work on the effects of early handling seems to be important for us in understanding drug effects.

Levine (5, 6) has been interested in studying some variants of this early handling. One of the variants he has studied is the effect of shaking rats as contrasted with early handling. Handling has some very special connotation relating a human to a rat; shaking doesn't. You put the rats in a shaker and you shake them, and Levine has tried to determine whether the same or different effects are found. As part of his research program, he has also tried

to find out what the differences are between young rats that have had such experience (handling, shaking, or whatever the variable is) and those that have not. One finding is that unhandled, unshaken subjects seem to show a delay in development as compared with those which are either handled or shaken. The effect of handling seems to be to speed up the achievement of normal maturational levels. These findings may have important implications for our understanding of child behavior.

Problems in Studying Children

When we now turn to the problems of drug effects in children, we have some which are similar to those encountered in other analyses of drug effects, and perhaps some different ones. I think we have systematically, and perhaps with malice aforethought, overlooked variables and events related to these variables which are important ones to note.

I am sure that those who have operated in a medical context, and most particularly in the context of the treatment of children, are aware of such things as the dose effect. We often talk about the effect of a drug as if there were a single effect independent of dose. This is one factor to consider. Second, in the administration of a given drug, the route of administration makes a difference. A third factor is that the physician, in spite of all the best controlled information and everything else that he has, must always be on guard for highly peculiar idiosyncratic effects.

I have a suspicion that medical students are beaten over the head with some of these notions. I have a further suspicion that pediatricians are especially beaten over the head about the utilization of drugs in the case of children as subjects.

Drugs of various kinds under medical supervision are being used with children. Drugs are being used for the spectrum of medical problems, and more recently for the treatment of emotional disorders. How wise such use is we really don't know, but we are concerned about this problem of drug utilization in children. We have a number of involvements which may permit us to examine our question in some other terms. Perhaps the most significant concern that we have in drug effects on the behavior

of children is with the problem of aftereffects. One thing that perhaps characterizes medical care of children as compared with other age groups is our concern that an event (a treatment) at some point in time early in life might have an effect (a negative effect) later in life. I am quite sure that such values enter into therapeutic decisions made by pediatricians and other physicians. It is precisely with this concern, dealing with the periods in the developmental life spans of a human, that we can center our major analysis.

Our central concern here is, of course, behavioral toxicity during and especially after drug therapy. The dimensions of this concern are as wide as what we know, or think we know, about children: social behavior, learning, motor development and performance, emotional behavior, etc. Dr. McCandless has indicated some of the ways in which these processes can be studied.

First let us consider the availability of subjects. Most frequently that portion of the population of children will be available for drug studies who are somehow or other categorized as requiring medical aid or are packaged in institutions. In this context of medical aid, drug studies can be done. The basis for such segregation of the total population is, as in the case of other behavior disorders, certainly socially relevant. By that I mean that aspects of the social and interpersonal behavior of a given child will have become so annoying, so obnoxious, so bizarre, so difficult to live with, that the child will be separated from his colleagues and placed in contact with technical experts of various kinds to be modified or to be stored. We must seriously concern ourselves with sampling problems and with follow-up of precisely such individuals who have been given drug therapy.

Another problem that we face, which I am sure is well known to every practicing pediatrician, is the problem of great caution with the use of any drugs in the treatment of children, particularly drugs which might have significant behavioral consequences. Here we probably face the problem of the special sensitivity of children to drug treatment, or the medical person's special sensitivity about drug treatment of children in general. In adults a similar problem exists. The analysis of the difference between

drug effects on hospitalized psychiatric patients and outpatients has been equally difficult to deal with. The hospitalized psychiatric patient (perhaps representing a much more severe social anomaly) is under direct medical supervision and can be manipulated in a wide number of ways, including exposure to drug therapy. The outpatient is, of course, a continuing member of his community and family, and must be treated with many other concerns for his own welfare. The effectiveness of drug therapy interacting with other sources of behavior modification might be quite different in these two instances. In the case of children, we would have the same situation, except that we have an even more significant concern for the future years of life that are presumably the property of this child now under treatment.

What can we expect out of a situation such as I have described? We certainly can expect that studies will be carried out cross-sectionally on institutionalized children to determine the behavior modification from the use of a variety of drugs. Some such studies have, of course, already appeared. We do expect that further studies will improve in design and control features. In the case of such "tagged" children, we have a real opportunity to follow up in future years.

Comparative psychological analysis with drugs is proceeding at this time at an accelerated rate. Some lines of research are closely related to the problem of the analysis of drug effects on children. We certainly can expect in the immediate future an even greater rate of increase of interest and work in the problems of developmental processes in infrahuman subjects. This type of research is catching on and is of apparent interest to a number of workers. We can hope that meaningful problems will be tackled and explored, and then quantified relationships determined so that appropriate transfer can be made to the human species.

We have the problem of trying to assay, to learn, and to discover the effects of drugs on events which we don't yet understand. We don't understand too much about how the drugs work. Coupled with this, we want to study the effects of drugs on behavior. We don't know very much about the behavior. This is a

pretty hard situation to face, but there are studies that can be done and that are being done, and I want to close on a note of hope.

There are ideas which are useful to manipulate—new ideas and, most frequently, old ideas. There are variants of established hypotheses that are worth re-asking. Fortunately, in all of the basic sciences related to these problems, valuable new techniques have been developed, so the problem isn't as bad as it sounds. For our time, with our level of ignorance, there are ways of attacking or approaching this problem. Many people can contribute in these attacks; whether they are going to be right or wrong, I don't know. The problem is worth pursuing, however.

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DISCUSSION

JONATHAN O. COLE

Dr. Ross, in his position as an experimental psychologist, has outlined a number of problems and very nicely described certain trends and shifts of emphasis in psychological research. Five years from now we may be able to hear not only papers on the effects of drugs on the development of young animals and children, but also papers on the effects of drugs on the development of psychological research.

My own position is that of a psychiatrist with both clinical and research biases. My clinical orientation is as much psychotherapeutic as it is pharmacotherapeutic, and although many of my research interests are pharmacological or biological, my emotional biases are psychodynamic. This puts me in an interesting midposition, able to pull the dirty trick of acting like a clinician around research people and like a researcher around clinicians. I don't think this is at all bad since it can often serve to broaden perspectives and perhaps to enable the Psychopharmacology Service Center to stimulate and help support both well designed clinical research and clinically relevant basic or animal research.

Dr. Ross has told us to expect an increasing amount of research on the psychological, behavioral, and neurophysiological stages through which animals pass during their growth and development. This work can be expanded to include studies of the effects of psychiatric drugs on these processes. This is well and good.

Without devaluating work of this sort, I would like to stress some of the problems which may arise as research findings concerning specific drug effects on specific developmental processes begin to appear in the scientific literature and begin to be mentioned and discussed in the lay press. There is danger that a finding that drug X given in a rat's childhood or puppyhood may make him both less intelligent and less anxious as an adult. Does this mean that clinicians should immediately stop using

drug X? Or, conceivably, that they should use it even more if they feel it is better for an adult to be less anxious and less intelligent than it is to be more anxious and more intelligent?

Even assuming that the dose of drug X given the rat was comparable to that given emotionally disturbed children, one still must worry about the dangers of overgeneralizing from the effect of a drug on a normal rat in a constant environment to the effect of a drug in an emotionally disturbed child in an environment that may well have helped produce his emotional illness. Similarly, generalizing from a normal rat puppy to a child with mild to moderate brain damage is equally hazardous.

This limitation in the generality of animal findings has two logical consequences: (a) more attention should be given to the effect of drugs on animals raised under stress conditions which in the absence of drugs would leave the animal "neurotic" or behaviorally abnormal at maturity, and (b) findings derived from animal work should, insofar as possible, be thoroughly rechecked in psychiatrically ill children if the drug in question has appeared to be clinically effective.

It is obviously highly unethical to study long-term drug effects in normal children. On the other hand, the practical clinical questions all pertain to sick children.

Dr. Ross in his paper has underlined the danger of "behavioral toxicity" occurring in children given drugs and has mentioned the possibility that drugs may interfere with learning.

My discussions with clinicians experienced in the use of drugs in children have led me to conclude that drugs, properly used, may greatly facilitate classroom learning in children who were previously too anxious, too confused, or too hyperactive to learn at all well. Good research should enable us to settle this highly important question, but it is certainly possible that a drug which interferes with learning in a normal growing rat or in a normal adult human may facilitate learning in an abnormal child. Some clinical observations and a controlled study reported by Freed (1) support this contention, but much more work is needed.

I would, therefore, like to stress that if overgeneralization is avoided, expansion and continuing interaction of drug research

in children with psychiatric disorders and in normal and abnormal young animals can be very profitable. Hypotheses arising in the clinic can often first be tested fruitfully in young animals, while findings derived from studies in young animals need to be verified through clinical research. More and better work in both areas is necessary for a better understanding of how psychiatric drugs act and how they can best be used in child psychiatry.

There is one other critical problem I would like to mention. Do children with psychiatric disorders really respond to different drugs, or differently to the same drugs, as compared to adults? The two current drugs which come to mind as apparently acting differently in children than they do in adults are Benzedrine and Benadryl. Well controlled clinical studies are needed to reconfirm earlier work on these drugs, and the lack of effectiveness of these compounds in adults with similar kinds of psychopathology should also be demonstrated conclusively. One can then move on to the intriguing question of why this difference exists. Do hyperactive children who respond to Benzedrine do so because of the developmental state of their central nervous system or because their central nervous system function has been altered by brain damage of some sort? Are drugs which work in impulsive, anxious, hyperactive children with short attention spans of any more value in adults suffering from impulsivity and severe personality disorders than in neurotic and schizophrenic patients who usually receive the more conventional psychiatric drugs?

The arrival of tranquilizing drugs has given a major impetus to the development of better research methods for the study of clinical change in adult psychiatric patients. Perhaps drugs will also impel us to find out more about the psychopathological, psychological, and neurophysiological similarities and differences between psychiatric illnesses found in children and those found in adults. Hopefully, in the next few years we will have not only a comparative psychopharmacology which will tell us about significant differences and similarities in drug response and in behavioral systems between various animal species and man,

but also a comparative psychopharmacology which will tell us about these kinds of differences and similarities between children and adults.

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Chapter 9

SOME NEUROPSYCHOLOGICAL PROBLEMS RELEVANT TO CHEMICAL INTERVENTION IN THE GROWING ORGANISM

LILA GHENT

THE TITLE of my paper is formidable, and I hope it does not appear to promise more than I can deliver. The question posed to me for discussion was: what can we learn about the central nervous system and integrative behavior from drug research with children? My point of view in dealing with this question is that of a physiological psychologist interested in a developmental approach to neuropsychological problems. I hope that my very naivete in the field of drug research in children will make it possible for me to have a fresh look at the problem—but, on the other side of this coin, I may pull some real boners.

The discussion is divided into three parts. First, I would like to consider drug research as one means of intervening in the central nervous system—chemical intervention in contrast to the more usual structural intervention of brain lesions—and discuss the kinds of questions that might be asked that are relevant to the relation between the brain and behavior. Given this general approach, I would then like to raise some problems that are specific to work with that charming but puzzling human subpopulation, children. Finally, I hope to show that research with children may give us leads concerning the relation between the brain and behavior that we would have been much less likely to come to if we had worked only with adults.

Intervention in Central Nervous System Functioning

A traditional way of investigating the relation between the brain and behavior is to study the effects of a lesion in a particular part of the brain on various aspects of behavior. In recent years,

a great deal of work has been done on the behavioral effects of frontal and of temporal lesions in the monkey, and these studies have consistently shown that a temporal lesion impairs some visual discrimination tasks whereas a frontal lesion impairs delayed response tasks (2). These data give us information about the frontal and temporal lobes, but in addition they tell us something about the processes underlying the two kinds of behaviors. From a psychological point of view, we could find similarities in the learning and memory processes presumably involved in visual discrimination and delayed response tasks, but the fact that the tasks can be selectively disturbed by different lesions indicates that the tasks involve different psychological functions.

The possibility of such behavioral analysis was pointed out by Lashley when he said, "The study of the effects of brain injury should serve as an alternative to factor analysis, parceling out elementary functions or abilities which may vary independently" (8, p. 155). Thus, instead of asking whether one part of the brain is linked with a particular behavior, we can consider the brain lesion as a technique for revealing those aspects of behavior that are linked together in the sense of being affected by the same neurophysiological system. Investigation of the associations and dissociations of behavioral defects caused by brain dysfunction could develop the psychological categories that are most relevant to neurophysiological processes. When the question is put this way—whether certain behaviors are disturbed together by a particular physiological change—then the locus of disturbance is not important, and chemical intervention in the central nervous system is as useful a tool as is surgical intervention.

To use a rather crude analogy, I am saying that if one did not have a map of the subway in New York, one could get some idea of the organization of the subway by interventions in its functioning. Let us say that we can observe the behavior of trains (their presence or absence) in a variety of stations, and that there is an interference in functioning at an unknown point. First we observe that there are no trains in the station at 7th Avenue and 14th Street, and then we find out that trains do not arrive at

two stations in the Bronx—Dyer Avenue and 242nd Street—and at two stations in Brooklyn—Flatbush and New Lots—whereas trains do arrive at certain other stations between Brooklyn and the Bronx. We would infer that the apparently unrelated stations at 14th Street and 7th Avenue, Dyer Avenue, 242nd Street, Flatbush, and New Lots did, in fact, belong to the same system, whereas other stations were not part of this system. A series of interventions in the functioning of the subway could provide a fairly good picture of the systems of connections in the New York subway.

Well, we are fortunate enough to have readily available maps of the subway system, but we are still using methods of intervention to map psychological and neurophysiological systems. I do not want to stress this approach as a method of choice, but simply as an approach that may be useful for problems that do not lend themselves readily to direct experimental analysis.

Psychologists do not usually do research by watching the behavior of subway trains, but we do watch the behavior of rats in Skinner-boxes. A rat can learn to press a bar in order to get food, to get water, to avoid shock, etc., and the behavior looks rather similar, at least superficially, under these various conditions. When the rat is given reserpine, however, Wenzel (10) found that bar pressing to avoid shock was impaired, whereas bar pressing for food was unaffected. Such data clearly indicate that reserpine does not affect learning as such, and that we should look for behavioral changes in other categories to define the psychological system affected by reserpine. This point may be obvious in the case of the rat, but in clinical studies the effects of drugs are usually described in terms of whether or not there are changes in learning, in emotion, in perception, etc. Instead of asking whether a drug affects these various categories, let us look at the grouping of behavior imposed by the drug itself ("factored out" in Lashley's terms) in order to develop a psychologically meaningful category.

The point I have been making is that one kind of question to be asked in drug research is whether a change in behavior A is accompanied by a change in B, or in C, and so on, and that such an approach will prove useful in delineating psychological

functions that are relevant to neurophysiological systems. To some extent, one does find associations of behaviors (although more by accident than by design) when one finds different aspects of behavior changed after the administration of different drugs. However, a listing of behavioral changes is only a first step, since such information still leaves us in the dark as to the relationship among the changes. Are these behaviors affected independently so that one cannot predict a change in one from knowledge of change in another, or is a change in one correlated with a change in another? For example, in drug research with children, does drug X have a generalized effect such that once the threshold for change is reached in one function, there is change in all functions? That is, if hyperactivity is affected, are there also changes in anxiety level, social relations, attention span, sleeping habits, etc.?

Since it is more likely that some effects will be selective, we can ask another type of question. In children in whom hyperactivity is affected, are sleeping habits more likely to be affected than in other children in whom hyperactivity is not changed? That is, do changes in hyperactivity and in sleep reflect a change in a common system?

Comparisons of various drugs can be made in terms of the observed associations of changes. For example, both chlorpromazine and reserpine may reduce hyperactivity, but one would want to know whether the changes associated with reduced hyperactivity were the same in both instances. In other words, do these chemically different drugs produce their effect on hyperactivity by acting on the same, or on different, systems?

The finding of associations of behavioral changes would have practical as well as theoretical importance. It may be that individual differences in response to drugs are such as to limit the prediction that a drug will always have a particular effect, but perhaps one will be able to predict that if effect A occurs, effect B will also appear.

There is another approach to the analysis of function that I want to discuss briefly, one that is unique to drug work and yet appears to have been relatively neglected. The use of drugs is characterized by repetition, and repetition may be accompanied

by the development of tolerance on the part of the organism. Despite the large numbers of repetitive doses of tranquilizing drugs that have been given, there does not appear to be much systematic information available on patterns of tolerance. That is, do some changes in behavior show adaptation to the effects of a drug more quickly than do other aspects of behavior?

As an example of the kind of information that could be obtained, a recent article by Freedman *et al.* (3) describes the development of tolerance to lysergic acid diethylamide in the rat. They found that adaptation occurred for a complex motor task—rope climbing—for pupillary dilatation, pyrexia, and piloerection, but not for bradycardia and respiratory arrest. These authors suggest that, since the loci in the brain for control of these various activities differ, perhaps the cortical and rostral brain stem centers adapt more readily than do centers in the caudal brain stem.

I think it would be of general theoretical interest to investigate the patterns of tolerance to different drugs, but such studies might also have some practical implications. The therapeutic usefulness of a drug might be related to a specific pattern of tolerance. For example, with continued use of a drug, it might be desirable for the autonomic effects to disappear in time, but it would be preferable for behavioral effects such as reduced hyperactivity to continue undiminished. Also, it would seem useful to develop tolerance to any intellectual and perceptual changes produced by drug action, but not to the emotional changes. Whether it is possible for such specific patterns of tolerance to develop is not known, although the problem is an interesting one and presumably possible of resolution.

Developmental Problems

Thus far I have discussed the kind of question that could be asked in drug work if one is interested in the relation between the brain and behavior. This approach is equally applicable to work with animals, with adult humans, or with children. Since we are concerned today particularly with children, I would like to focus now on some problems that are specifically added by

the parameter of growth. It would be surprising indeed, although important to know, if the effects of tranquilizers were the same at all ages. Would we expect different functions to be affected at different ages? Would we expect the younger child to be more vulnerable, or to be less vulnerable, to the effects of various drugs?

If we look to embryology for a moment, where the method of chemical intervention in the growing organism has been in use for a long time, we find some tentative answers to these questions. It is clear that the effect of a given substance varies, depending on the age of the organism. For example, the injection of insulin into the chick embryo from 0 to 60 hours after incubation produces a rumpless chick, whereas the injection of insulin between 70 and 160 hours produces micromelia (7). On the other hand, at a given age, different substances may have different effects, indicating some specificity in the interaction between a particular substance and developmental level. One generalization derived from such work—with many exceptions to the rule—is that a structure is most sensitive to disturbance during the formative stages, when the cells are as yet undifferentiated, or when the structure is being most actively elaborated (11). One of the corollaries to this generalization is that the younger the organism, the more generalized or profound will be the alterations produced.

Can we also say, for the psychological and physiological functions in which we are interested, that intervention in the central nervous system will produce alterations that are more profound, or more generalized, in the younger organism? Some data suggest that the opposite may be true. For example, injury to the motor cortex (6) or to the visual cortex (9) of the infant animal is less deleterious to motor and visual functions than a comparable lesion in the adult animal, suggesting greater resiliency of the infant nervous system. On the other hand, those investigators who have been interested in the effects of infant brain injury on adult intelligence have noted that injury to the infant brain is followed by more generalized and severe effects than is brain injury at a later age (4). Of course, the question is oversimplified as I have put it, since the effects of intervention are probably not

the same for all functions. However, what I want to say is that study of drug effects in children can contribute to the question of the relative vulnerability of a variety of functions, or of any given function, at different stages of development.

The last question I would like to raise in this section is whether an addictive type of process, or "habituation," is more likely to occur at one age than another. Although there is no evidence of which I am aware to indicate that the young organism would develop dependence more readily than an older organism, it is not unreasonable to suppose that a system which develops under certain conditions would be dependent on those conditions for optimal functioning. For example, there is the rather unusual case report (5) of an infant whose mother had taken large doses of pyridoxine during the first five months of pregnancy. As might be expected, the mother showed no signs of pyridoxine addiction or dependency. However, a few hours after birth the baby began to convulse. Study of the infant for several months revealed that the convulsions could be controlled only by the administration of pyridoxine. The authors considered the problem to be one of pyridoxine dependency. No doubt this particular case is a complicated one, and while development of dependency may not be the only interpretation possible, it is nevertheless a very credible one.

The implication for drug work with children is that, if the functioning of some psychological systems is dependent (using the term loosely) on the particular physiological conditions in which they were developed, then the very young child would be more likely to show signs of habituation than the older child or adult. A theoretical framework which is consistent with such a possibility is the neuropsychological theory developed by Hebb (4), describing how cell assemblies (i.e., patterns of firing which are the neural counterparts of concepts) could be organized through the experiences of the organism. In the adult, and presumably the older child, the cell assembly has a large margin of safety; that is, N cells might have been originally active in the assembly, but the synaptic facilitation between cells is increased through use such that at a later age only $N - a$ cells are necessary

for maintenance of the pattern of firing. Thus, well developed cell assemblies would show stability in the presence of a chemical agent that changed neural activity in some way, and furthermore the established cell assembly would incorporate relatively little of the changed pattern of activity.

One consequence of this would be that when the drug was withdrawn, it would have little effect on the functioning of the assembly. In the young child, where cell assemblies are in the process of being formed, it is possible that the changes in neural activity induced by chemical agents would be incorporated as part of the development of the cell assembly. Thus, one would expect that symptoms of habituation in the area of perceptual and intellectual performance would be more likely to appear in young children than in older children and adults. I have stated this possibility in an extreme way, and while it is unlikely that gross habituation would appear, a search for subtle effects would be of theoretical and clinical significance.

Incidentally, there is a problem implied in this whole discussion of the relation between age and drug effects that I would like to make explicit. Since we have so little information in this area, it is possible that tranquilizing drugs have a deleterious effect on some aspects of growth and development. I feel most strongly that this problem should be dealt with before we can undertake to explore other aspects of the relation between drug action and the stage of development of the organism.

Developmental Approaches to Brain-Behavior Relations

I would now like to cease asking questions for the sake of posing problems, and instead ask a question for the purpose of illustrating an answer. If we are interested in the relation between the brain and integrative behavior, is there any special value in studying the behavior of children? I am sure that a great many people would say, "Yes, of course, the more we understand the development of any particular aspect of behavior, the better we will understand the functioning of the adult organism." The way in which this general principle is most usually applied is in the regression hypothesis. According to this point of view,

the manifestations of disturbances in function in the adult, from brain injury to schizophrenia, are considered to reflect a regression to autogenetically earlier modes of functioning. I myself do not favor the regression hypothesis, although it can serve as a very useful shorthand for describing and categorizing behavior.

The point of view that I would like to illustrate now is that work with children may suggest fresh questions to be asked about the behavioral defects observed in the adult. That is, I am not going to draw any parallels between disruption of behavior in the adult and childlike behavior. Instead, I would like to show how a problem that was first raised in adult behavior was investigated developmentally, and that the developmental data then suggested a new line of inquiry into the adult phenomenon.

One of the disturbances reported to occur after brain injury in the adult is a difficulty in handling visuomotor material. Dr. Bender has worked on this problem (1), and the Bender-Gestalt test, the Kohs Block Designs test, etc., are frequently used to measure disturbance in visuomotor functioning. One aspect of this visuomotor difficulty is that, although a form may be reproduced accurately, its spatial orientation is changed. Some difficulty in reproducing the orientation of forms is also characteristic of normal young children, and so it seemed worth while to study the normal development of the response to spatial orientation as one way of approaching the deficit shown after brain injury.

There were a variety of ways in which I set out to study this problem; what I want to tell you about is a way that I had not planned, but came upon by chance. In doing some exploratory work, I asked four-year-old children to tell me which of a pair of realistic forms was upside down, and of course they could do this quite well. When I included pairs of nonrealistic forms, such as a crescent, a V-shape, an incomplete circle, etc., and asked which was upside down, the children of pre-school age did not find the request a strange one. More importantly, they showed remarkable agreement as to which spatial orientation they considered to be upside down. Questioning of the children indicated that they were not choosing on the basis of considering

the geometric forms to be representative of realistic forms. Sometimes they would ask what the picture was supposed to be, while in the next breath they said that one of two unidentifiable forms was upside down. This preference for orientation of nonrealistic forms is a fascinating phenomenon, but I want to consider it now only with respect to its implications for disturbances in visuomotor functioning in the adult.

Why is it that a nonrealistic form looks "right" to a child in a certain orientation and "wrong" in any other orientation? One possibility is that recognition of the form is facilitated by a particular orientation. If we assume that the young child does not perceive a figure as readily as an adult and that the figure is scanned or perceived sequentially, then perhaps this sequential perception is facilitated when the form is in a particular position rather than in other positions.

The rotations noted in the reproduction of forms after brain injury have usually been interpreted as indicating an instability in the subject's space perception or a defect in the actual perception of spatial relations. The work with the children suggests a very different interpretation. Perhaps the figures are rotated when they are not in the perceptually preferred position (i.e., the position that facilitates sequential perception and sequential reproduction of the form). One could make a first step toward testing this hypothesis by simply asking the subject who rotates forms to put the forms in the position that looks right to him to see whether the perceptually right position corresponds with the spatial orientation in which the form was reproduced. The next question one might ask is whether the recognition of a form—not the reproduction but simply the identification—is better when the form is in one orientation than in another.

Although this problem intrigues me a good deal, I shall not burden you further with my ruminations upon it. The purpose of this discussion has been to illustrate the way in which study of a problem in children may suggest new approaches to the same problem in the adult. Speaking more generally, if we know how a given behavior has been put together, then we may understand the dimensions along which the behavior can fall apart. Instead of considering certain disturbances in behavior as a regression

to a more simplified mode of functioning, we can ask along which particular dimensions simplification or change has taken place.

Summary

I would like to recapitulate very briefly the main points of the discussion. Chemical intervention in the central nervous system provides the opportunity for investigating whether apparently similar or related behaviors can be separated and, conversely, whether dissimilar behaviors do in fact belong to the same neurophysiological system. There are some particular questions to be asked in work with a developing organism. Are psychological functions more resilient during the developing stages than after the function is established? Is the young organism more vulnerable to a habituating type of process than is the older organism? Finally, discovery of the factors underlying behavior at different stages of development may suggest the dimensions along which behavior is changed as a result of brain dysfunction.

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DISCUSSION

JOEL J. ELKES *

Dr. Ghent has done us all a service in defining some of the islands of knowledge as well as the massive ignorances which at present bestride this inordinately difficult field. In a sense, the questions she posed recall the very questions posed by the First International Neurochemical Symposium on the Biochemistry of the Developing Nervous System, held at Oxford in 1954. The editor of the proceedings of that symposium chose this quotation by Sherrington as the motto of the conference: "... the problem has one virtue at least—it will long offer to those who pursue it the comfort that to journey is better than to arrive" (6, p. v). To be sure, in this field of developmental neuropharmacology or neurochemistry, we are in for an interesting, if bewildering, journey. It is always much more interesting (and infinitely more difficult) to study imbalance as against balance, change as against stability. The time scale of morphological change in the developing nervous system is, despite its rapidity, infinitely slower than the time scale of chemical change, and the experimentalist's hand must indeed be swift to define such change.

One issue posed by Dr. Ghent is the potential value of discrete chemical intervention in determining the connectedness and relatedness of functional systems within the nervous system. It is this connectedness which is so often missed by an exclusive study of one function out of context with another. As

* Illness prevented Dr. Elkes from attending the conference. These comments were prepared subsequently for inclusion in the present volume.—Ed.

she says, functions cluster and group themselves during critical developmental periods, when (to change the metaphor) the information genetically stored in the nervous system is activated in quite specific (and often stimulus-bound) directions. This is well known at a relatively crude level such as the emergence of the various reflex patterns in man. Equally, it has been studied in laboratory animals, where (in the rat, for example) the appearance of reflex functions adheres to a definite and reproducible temporal sequence (1, 2). Though such patterns have been established, very little indeed is known of the interrelatedness of these various patterns.

To add force to Dr. Ghent's point of the inordinate stability of some of these functions in the face of chemical intervention, I can but quote a brief series of exploratory experiments performed by my colleagues in Birmingham some five years ago (3). We tried to study the effects of a number of drugs on postnatal development in the rat by administering them (in most instances twice weekly) from the 6th to the 40th day of life, and in some instances for 150 days. The drugs used were some anticholinesterases (including DFP, iso-OMPA, and TCP*), d-amphetamine, lysergic acid diethylamide and dihydroergotamine, chlorpromazine, and picrotoxin. Eye opening, the startle reaction, the air-righting reaction, the placing reaction, reflex suspension, and sensitivity to an electric stimulus were tested daily. In the case of the anticholinesterases, levels determined at different ages were compared with littermate controls receiving arachis oil (the vehicle) and atropine only.

Although the dosage of the anticholinesterases was severe enough to cause death of nearly a third of a total of some 150 animals, the chronic administration of cholinesterase inhibitors affected growth only slightly, and did not in any appreciable way affect the time of appearance of the body-righting, air-righting, or placing reactions. There was a relative freedom of postinjection neurological symptoms around the 25th to 40th day, and a gradual change in the pattern of symptoms during the period from the 40th to the 100th day of life. We thought

* These three agents are, respectively: di-isopropyl fluorophosphate, iso-octamethyl pyrophosphoramidate, and tricresylphosphate.—Ed.

at the time that the results pointed to different rates and patterns of development of the enzyme during these two periods of development (4). Although it seemed doubtful whether the high cholinesterase inhibition figures obtained (which were of the order of 70 per cent) reflected the inhibition *in vivo*, the results suggested either a very high reserve for the cholinesterases in the rat's central nervous system or a lack of dependence of the processes studied upon these enzymes. Equally, one wondered then, and one still wonders, whether substrates other than acetylcholine may well have operated in this process. I would, however, wish to stress again the relatively crude nature of the indicators used in this study.

The enigmatic findings obtained with the other drugs posed several problems, of which perhaps two deserve mention. First, while growth was significantly retarded by all the drugs employed, such statistical trends as were apparent in our small samples suggested an advancement in time of some forms of behavior by some of the drugs tested. Secondly, no single drug exerted a universal effect on all phenomena studied. A differential effect of the drugs on the emergence of responses therefore seemed at least possible. Naturally, one cannot in any way claim that the tests used in this limited series (of some 56 animals) measured the maturation of specific centers or nuclear groups in the central nervous system. Too little was known to us at the time in this respect. Equally, we were limited to a study of sequential emergence of certain reflexes. It is a totally different matter to ask whether such persistent chemical intervention would interfere with either memory or learning. Rosenzweig has some important clues in this respect in the work which he has recently communicated (5).

It would seem to me that careful use of specific enzyme inhibitors (particularly directed against enzymes either known to have, or suspected of playing, a vital role in the economy of the developing nervous system) may give us valuable clues as to the relation of a particular enzyme system (and its appropriate metabolite) to the development of a group of functions, the latter, in turn, depending upon the maturation of appropriate cell groups. Equally, if discrete chemical intervention proved

successful, it might contribute to an understanding of the release of patterns of behavior during the maturation of the endocrine apparatus and give the storage and release of such patterns a more precise chemical connotation.

Dr. Ghent also referred to the concepts of regression. I agree emphatically that the regression to older patterns of adaptive behavior, a sort of Jacksonian march in reverse, is too simple a scheme and does not take account of the novel and unique way in which the functions of the nervous system adapt to change. Again, in this respect drugs may teach us a good deal—drugs used singly, or drugs used in combination.

Lastly, I would ask Dr. Ghent whether at this stage of our knowledge we are at all justified in assuming that the storage and processing of information occur in cell assemblies as the penultimate units, or whether the dynamic turnover-in-time of subcellular constituents may not have something to do with our ability to store and process information and, more particularly, our inordinate ability to process information in time. Is it at all likely that the neuroproteins may be a rather special kind of information storing protein, distinct from the genes which firmly and indelibly store hereditary information, or the immune bodies which store information over a long span of time? Somehow the nervous system appears to be especially adapted to processing information in short bits of time—in fact, the ability to organize time in the service of adaptive response would seem to be an outstanding property of nervous tissue. Can we be sure that it is the neuron and the neuron assembly which play a part in these lightning transactions? Could not tracer studies give us more insight into the turnover of subcellular constituents and their possible changing pattern with development? Again, I feel discrete interference with pharmacological agents in the developing nervous system may pave the way for fruitful work in this area.

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Chapter 10

CLOSING REMARKS

MILTON J. E. SENN

I WOULD LIKE to close with the words that Dr. Ross has just used about "beating the heads" of pediatricians. I will now expose my own biases and prejudices. One of the advantages of coming to a conference like this is to be stimulated and to be provoked and to find agreement and to find companions in one's own despair.

My concerns are in connection with nonpsychiatric and psychiatric physicians who now misuse drugs. I would beat all physicians over the head for the way they are presently using drugs, aided and abetted by the drug companies.

There are drug company representatives here today. I would make a few pleas to them. First of all, do not encourage the nonpsychiatric physician to use drugs when other areas of psychotherapy are needed, useful, indicated.

We are seeing today a change in medicine. The pediatrician is now even more concerned with behavior than ever before. He is often called upon to deal with children who are not psychologically sick in terms of mental illness, but who are disturbed enough that the parents want help—at least diagnostic help, and maybe help for their own anxiety. The pediatrician and the nonpsychiatric physician are now attempting to use drugs as short cuts they have been seeking for years to bring about changes in behavior that parents expect the physician to bring about.

I think the drug houses are aiding and abetting this by their looseness of advertising and by the frequency with which they send out literature and samples. I beg them to save their own money, save our time, and not send out as much material as they do. And when it is sent out, the drug companies should suggest more caution to the physician so that he will not use the drugs recklessly.

The other thing I would like to point out is that I appreciate very much the words of caution offered today by the research workers, words of caution to the clinician that he should use sharper hypotheses and better designed experiments as he proceeds in the area of clinical investigation.

Finally, a number of you—Dr. Ghent, Dr. Ross, Dr. Long—have mentioned the value of the child as a subject for research, and this I agree with; yet I cannot understand why more psychologists do not become interested in child study and why they do not join their medical colleagues in collaborative studies.

I know some of the reasons why this is not done. For example, it is not easy to translate and interpret from one discipline into another. There is, in addition, the difficulty of dealing with different species. One of America's foremost psychologists, having recently spent a year in an attempt to write a book on comparative psychology, said to me, "I have decided that my colleagues over the years are right. There is no such thing as comparative psychology." I think that possibly his dilemma came about because he was looking for similarities of behavior in different species. As Dr. Ross pointed out, we must also look for differences when we concern ourselves with comparative behavior.

Finally, to close my remarks, Dr. Fisher suggested that I might tell you something about some of the important similarities between American research in human behavior as it relates to animals and children and the research now being carried on in Russia. As some of you may know, I spent some time there during the past year, and really to review their research would be a long paper in itself. So, I will only say that in Russia it is easier to study children than it is in this country. Almost every department of pediatrics has a group of orphans in residence; they are under three years of age and are available for all kinds of investigative studies.

The tranquilizers are used in Russia because the Russians believe there is only one real cause for psychological difficulty, and that is the organic—rheumatic fever, encephalitis, poor conditioning, endowment, etc.; hence, their interest in the use of drugs that will change organic pathology.

Chapter 11

REFERENCE LIST ON THE USE OF PSYCHOPHARMACOLOGICAL AGENTS WITH CHILDREN

LORRAINE BOUTHILET and SEYMOUR FISHER

THIS REFERENCE list, and the accompanying index, is made up of studies of the effects of psychopharmacological agents with children. The references are mainly concerned with drugs used in psychiatric practice for therapeutic purposes. In order to keep the list to a reasonable length and more directly related to the problem at hand, we excluded studies of such agents as glutamic acid, anticonvulsants, barbiturates, etc. A reference list of this kind could clearly have included other articles and been extended in many directions. We have here attempted to give a selected compilation of the published literature which, in our opinion, is most relevant to the psychopharmacological research in this field.

The references are limited to published articles (and some papers read at meetings) in the English language. Reports on psychopharmacological research with children have, of course, appeared in other languages, notably the early article on the use of chlorpromazine with children by Heuyer, Giraud, and Galibert, "Traitement de l'excitation psycho-motrice chez l'enfant par le 4560 R. P.," published in the *Archives Françaises de Pédiatrie* in 1953. However, for practical reasons, it was decided not to attempt to include the foreign literature.

The references may be divided into two general types of studies: (1) those specifically and directly concerned with children, and (2) those in which some of the subjects are children, but in which the study of children is not the primary aim of the research. The articles specifically dealing with research on children are annotated; the others are not. It should be empha-

sized that the annotations are brief indicative notes, attempting to reflect the content of the article with no evaluation or other critical editing.

The list was compiled from articles and documents in the Technical Information Unit * of the Psychopharmacology Service Center, which maintains a collection of articles relevant to the field of psychopharmacology.

In preparing the index to the reference list, we made no attempt to analyze the subject matter in any detailed fashion. Rather, our more modest goal was to select a small number of categories which would be meaningful and useful to the reader in his search for particular kinds of studies. Also, instead of alphabetizing the various headings used in the index to describe a study, we decided to group the terms under the following categories: (a) type of reference; (b) type of child; (c) clinical setting; (d) follow-up; (e) drug; (f) dependent variables; (g) type of measure; and (h) side effects. This index is not intended to be either exhaustive or definitive; we do hope, however, that it will be a convenient time-saver in directing the reader to the studies in which he is most interested.

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2. Addison, R. G.: A preliminary report on the use of chlorpromazine hydrochloride in a correctional institution. *Psychiatric Quart.*, 30:15-22, 1956.
3. Allen, M.: The value of Compazine in the management of psychotic female adolescent mental defectives. In report on prochlorperazine. *Proceedings of the regional conference of Southern California Neuropsychiatric Hospitals*, June 28, 1957. New York, Nerv. & Ment. Dis. Monographs (Physicians Postgraduate Press), 1957. Pp. 19-20.

The effects of prochlorperazine were investigated in 23 mental defectives,

* We should like to acknowledge the valuable assistance of Helen Chandler, Carmen Eldridge, Miriam Geller, Florence Hall, and Alberta Jarvis.

aged 8 to 18, who were psychotic or had behavior problems. Of the psychotics, six showed a good response, two fair improvement, and one had to be discontinued. Of the children with behavior problems, one was discontinued, eight improved, and five remained unimproved. Of the two children for whom medication was stopped, one had developed a fine tremor in the hands, and the other had marked drooling.

4. Allin, T. G., Jr., and Pogge, R. C.: The use of azacyclonol and pipradrol in general practice. *Int. Rec. Med.*, 169:222-230, 1956.

In this review two paragraphs are devoted to the pediatric uses of pipradrol. Two references are cited which report that it is beneficial in treating children with behavioral disturbances and those with enuresis.

5. American Medical Association. Foreign letters. Peru: Tranquilizers. Drug therapy for infant psychiatry. *J.A.M.A.*, 165:1472-1474, 1957.

This report on a symposium on the use of tranquilizers in psychiatry, held in Lima, Peru, includes a summary of Dr. Emilio Majluf's brief remarks on drug therapy in pediatric psychiatry. He describes the dosage and effects of various drugs (diphenhydramine, chlorpromazine, promethazine, mephenesin, glutamic acid, promazine) in infants and children whose disorders ranged from restlessness to mental retardation, psychosis, epilepsy, and cerebral palsy.

6. Andermann, K.: Electroencephalographic evidence of personality changes produced by ataraxic drugs in mentally disturbed patients. *M.J. Australia*, 2:1-8, 1957.

7. Anonymous. Child psychiatry and the general practitioner. *M. Times*, 84:689-698, 1956.

Directed to the general practitioner, this "refresher article" on child psychiatry covers etiology, diagnosis, symptomatology, psychosis, prophylaxis, and treatment, including the use of various drugs (barbiturates, antispasmodics, antihistamines, tranquilizers, antidepressants, and others).

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10. Asung, C. L., Charcowa, A. I., and Villa, A.: Effects of a new

tranquilizing drug (Nostyn) on the behavior patterns of children recovered from tuberculous meningitis. *Quart. Rev. Sea View Hosp.*, 16:80-85, 1956.

The effects of ectylurea were investigated in nine children who were mute, deaf, mentally retarded, or presented behavior problems following recovery from tuberculous meningitis. A case summary is presented for each patient. The drug had a relaxing effect on hyperactivity, spasticity, and insomnia. In some cases improvement was maintained after the drug was stopped, but in most cases the symptoms recurred.

11. Asung, C. L., Charcowa, A. I., and Villa, A. P.: A study of the nonhypnotic calmative effective of 2-ethylcrotonylurea (Nostyn) in children with behavior problems. *New York State J. Med.*, 57:1911-1914, 1957.

This is a report of a clinical study of the effects of ectylurea on hyperexcitable, uncooperative, or antisocial behavior patterns of 51 children, aged 2 to 12, who were difficult to manage in a hospital pediatric service. Fairly detailed results are reported, including effects after the drug was stopped, effect on enuresis, response of patients with postmeningitis behavior problems and patients requiring minor operative procedures, effect of increased dosage, and influence on weight. Over-all, the drug effectively normalized 35, was of minimal or questionable value in 8, of no value in 4, and adversely affected behavior in 4. No toxic effects were seen.

12. Ayd, F. J., Jr.: A clinical evaluation of Frenquel. *J. Nerv. & Ment. Dis.*, 124:507-509, 1956.
13. Ayd, F. J., Jr.: Emotional problems in children: the uses of drugs in therapeutic management. *California Med.*, 87:75-78, 1957.

The author discusses the uses of phenobarbital, meprobamate, hydroxyzine, chlorpromazine, and reserpine in the treatment of various emotional disturbances of children. It is emphasized that drug therapy is a part of the total therapeutic attack on the emotional problems of children.

14. Ayd, F. J., Jr.: Meprobamate therapy for convulsive disorders of children. *Bull. Sch. Med. Univ. Maryland*, 42:2-5, 1957.

A one-year clinical trial was undertaken to investigate the anticonvulsant properties of meprobamate in 25 outpatient children with epilepsy refractory to other compounds. Physicians, parents, teachers, and school nurses recorded seizure frequency and undesirable side effects. Results are discussed in terms of type of epilepsy and indicate that meprobamate is of little value in grand mal epilepsy but that it is effective in reducing the

frequency of petit mal and myoclonic seizures. Side effects were drowsiness, tremor, incoordination, nausea, and one case of severe generalized dermatitis which required immediate withdrawal of the drug.

15. Bair, H. V., and Herold, W.: Efficacy of chlorpromazine in hyperactive mentally retarded children. *A.M.A. Arch. Neurol. & Psychiat.*, 74:363-364, 1955.

The effects of chlorpromazine in 10 hyperactive mental defectives were compared with 10 untreated children who were matched with the drug-treated group for age, sex, and IQ. Test-retest IQ (Columbia Mental Maturity Scale) showed an increase of 10.4 points in the drug-treated group as compared to an increase of 2.5 points in the untreated group. Behavioral improvement also occurred as a result of drug therapy. No side effects were observed.

16. Baird, H. W. III, and Borofsky, L. G.: Infantile myoclonic seizures. *J. Pediat.*, 50:332-339, 1957.

This paper reports a study of 80 children whose EEG's showed hypsarrhythmia, 51 of whom had infantile myoclonic seizures either alone or in addition to another convulsive disorder. Various additional symptoms are described. The administration and effects of a number of drugs (meprobamate, phenobarbital, acetazolamide, and others) are reported. In general, drug therapy was unsatisfactory in controlling infantile myoclonic seizures, although meprobamate showed some promise.

17. Baird, H. W., Szekely, E. G., Wycis, H. T., and Spiegel, E. A.: The effect of meprobamate on the basal ganglia. *Ann. New York Acad. Sc.*, 67:873-884, 1957.

Following a report on experimental studies with cats, the authors review their studies of the effects of tranquilizers on the subcortices of children who had extrapyramidal and/or convulsive disorders.

18. Bakwin, H.: Benzedrine in behavior disorders of children. *J. Pediat.*, 32:215-216, 1948.

Amphetamine is reported as a useful aid in the treatment of disturbed children. The author notes that it should only be used as an adjunct to adequate psychotherapy since it does not remove the source of conflict which led to the difficulty. No serious side effects were noted.

19. Bakwin, H.: The uses of chlorpromazine in pediatrics. *J. Pediat.*, 48:240-247, 1956.

This review of the literature covers the pharmacology and toxicology of chlorpromazine and its uses in children. Twenty-two references are cited.

20. Barsa, J. A., and Kline, N. S.: Use of reserpine in disturbed psychotic patients. *Am. J. Psychiat.*, 112:684-691, 1956.
21. Basmajian, J. V., and Szatmari, A.: Chlorpromazine and human spasticity. An electromyographic study. *Neurology*, 5:856-860, 1955.
22. Becattini, U., and Gallini, R.: Clinical evaluation of the action of meprobamate, benactyzine and hydroxyzine in the treatment of some psycho-emotional juvenile disorders. In S. Garattini and V. Ghetti (Eds.), *Psychotropic Drugs*. Amsterdam, Elsevier Publishing Company, 1957. Pp. 563-564.

Three groups of university students suffering from psychoemotional and anxiety disorders were treated with meprobamate, hydroxyzine, and benactyzine. Good results were achieved with meprobamate and hydroxyzine; no serious side effects were noted. Benactyzine proved to be less effective than the other two drugs.

23. Benda, C. E.: The differentiation between mental deficiency and emotional disorders, and some therapeutic experiments with *Rauwolfia serpentina* whole root (Kogluroid). *Arch. Pediat. Uruguay*, 26:32-46, 1955.

In differentiating between mental deficiency and emotional disorders, the author discusses pediatric psychiatry in general and devotes special attention to the autistic child and childhood schizophrenia. Three fairly lengthy case histories are cited in which treatment with *rauwolfia* whole root brought about marked improvement in behavior and adjustment. The author's experiences in treating more than 10 children with *rauwolfia* whole root are summarized.

24. Bender, L.: Treatment of juvenile schizophrenia. In *Neurology and Psychiatry in Childhood*. Baltimore, Williams and Wilkins, 1956. Pp. 462-477. (Also, *A. Res. Nerv. & Ment. Dis., Proc.*, 34.)

This review and the discussion following it include only very brief, general comments on drug therapy with children.

25. Bender, L., and Cottington, F.: The use of amphetamine sulfate (Benzedrine) in child psychiatry. *Am. J. Psychiat.*, 99:116-121, 1942.

The authors discuss the use of amphetamine sulfate with children with psychoneuroses, neurotic behavior disorders, psychopathic personalities, schizophrenia, and organic brain disease.

26. Bender, L., and Nichtern, S.: Chemotherapy in child psychiatry. *New York State J. Med.*, 56:2791-2795, 1956.

The authors review some of their own experiences and much of the literature on the use of drugs in children, referring to diagnosis, symptoms, dosage, and prolonged use of drugs, and comment on the value and effectiveness of particular drugs. Forty-seven references are cited.

27. Berman, H. H., Lazar, M., and Noe, O.: Prochlorperazine as an antiemetic in the severely retarded child. *A.M.A. J. Dis. Child.*, 95:146-149, 1958.

The small number of children (35) investigated and their abnormal mental, physical, and neurological states (8 with vomiting associated with subacute or chronic infection of the gastrointestinal or respiratory tract, 10 with associated CNS disease, and 14 who were habitual hand or tongue suckers or in whom there were psychic causes, e.g., severe anxiety) does not permit conclusive assessment of prochlorperazine as an antiemetic in all children. It would appear, however, that the drug is fairly effective in vomiting associated with psychic phenomena.

28. Berman, H. H., Lazar, M., Noe, O., and Schiller, H.: Pentylene-tetrazol (Metrazol) in mental deficiency. *A.M.A. J. Dis. Child.*, 94:231-233, 1957.

Using an own-control design, the effects of pentylenetetrazol were investigated in a total of 121 mentally defective children. Evaluation was based on a 69-item rating scale. There was no significant change in behavior which could be attributed to the drug, nor was there any change in intellectual functioning.

29. Berry, R. V., Kamin, S. H., and Kline, A.: An unusual complication following the use of Trilafon in children. *U. S. Armed Forces M. J.*, 9:745-750, 1958.

Case reports of two children who reacted to three 4-mg. doses of perphenazine in a bizarre manner. The outstanding symptom was peculiar cataleptoid status with the phenomenon of "waxy flexibility." The authors emphasize the fact that considerable caution should be used in the administration of tranquilizers, especially in children.

30. Bleiberg, J.: A preliminary report on a new approach to the treatment of acne vulgaris. Paper read at Hoffmann-La Roche, Inc. Symposium on the biochemical and clinical aspects of Marsilid and other monamine oxidase inhibitors. New York, November, 1957.

31. Block, S. L.: Effect of mephenesin upon anxiety. *A.M.A. Arch. Neurol. & Psychiat.*, 69:727-731, 1953.
32. Bonafede, V. I.: Chlorpromazine (Thorazine) treatment of disturbed epileptic patients. *A.M.A. Arch. Neurol. & Psychiat.*, 74:158-162, 1955.

The effects of chlorpromazine were investigated in 78 disturbed epileptics, 17 of whom were between 12 and 20 years of age. Some of the patients were psychotic. Results are discussed in detail. In general, chlorpromazine was very effective in controlling behavior disturbances, but it did not appreciably reduce the frequency of seizures when maintenance therapy with phenobarbital or diphenylhydantoin was reduced. Complications included fever, constipation, macular or maculopapular rash, coarse tremors of the upper extremities, drooling, ringing of the ears, two cases of jaundice, and two cases of eosinophilia, and coma and death in one patient on a daily dosage of 400 to 600 mg. chlorpromazine. A brief case report is given for a 13-year-old.

33. Bonello, F. J.: Chlorpromazine in general practice. *Int. Rec. Med.*, 169:197-212, 1956.

The author reports his impressions, based on a 15-month period, of the effects of chlorpromazine on outpatients and hospitalized patients. One section of the paper is concerned with pediatric uses of the drug. Among the cases treated were children with severely agitated behavior disorders, cerebral palsied children, children with idiopathic convulsive seizures, and cases of dysmenorrhea and tension occurring at the menarche. He also reports the use of chlorpromazine to control nausea and vomiting in infants and children with gastroenteritis and states that the drug is used routinely pre- and postoperatively in children undergoing minor or major surgery. Side effects are reported. A case report is given of a 17-year-old girl who developed an urticarial reaction to the drug.

34. Bower, H. M.: A clinical evaluation of reserpine in the treatment of chronic mental patients. *M. J. Australia*, 42:82-86, 1955.
35. Bower, W. H.: Chlorpromazine in psychiatric illness. *New England J. Med.*, 251:689-692, 1954.
36. Bradley, C.: The behavior of children receiving Benzedrine. *Am. J. Psychiat.*, 94:577-585, 1937.

The psychological reactions of 30 behavior problem children who received amphetamine sulfate for one week were observed. There was improvement in school performance in half of the children. A large proportion

of the patients became emotionally subdued without losing interest in their surroundings. A variety of other behavior changes are also noted. Dosage, unfavorable responses, and duration of effect of the drug are discussed.

37. Bradley, C.: Problem children: electroencephalographic psychological treatment. *Connecticut M. J.*, 6:773-777, 1942.

The practical application of the knowledge concerning electroencephalography for diagnosis and several drugs, particularly amphetamine sulfate, for the treatment of children's behavior disorders is discussed and a case report illustrating their use is appended.

38. Bradley, C.: Benzedrine and Dexedrine in the treatment of children's behavior disorders. *Pediatrics*, 5:24-37, 1950.

Twelve years' experience with amphetamine and d-amphetamine sulfate as a treatment for childhood behavior disorders is reported. The conclusion is drawn that these drugs influence children's behavior by altering their emotional reactions to distressing situations.

39. Bradley, C.: Tranquilizing drugs in pediatrics. *Pediatrics*, 21:325-336, 1958.

A tentative classification of tranquilizing substances, their general effects, probable mode of action, and potential hazards are discussed. Included is a brief review of the literature. Indications for use and some of the principles of effective administration are outlined. Emphasis is placed on the fact that tranquilizers may be useful for relief of symptoms, but that in the treatment of emotionally disturbed children psychological management should also be employed.

40. Bradley, C., and Bowen, M.: School performance of children receiving amphetamine (Benzedrine) sulfate. *Am. J. Orthopsychiat.*, 10:782-788, 1940.

The effect of amphetamine sulfate upon schoolroom behavior, arithmetic performance, and spelling performance of 19 institutionalized elementary school children was analyzed. Improvement in arithmetic performance was striking in nearly all cases. The effect on spelling performance was variable, with notable improvement in some cases and actual diminution of work in others.

41. Bradley, C., and Bowen, M.: Amphetamine (Benzedrine) therapy of children's behavior disorders. *Am. J. Orthopsychiat.*, 11:92-103, 1941.

The effect of amphetamine sulfate upon the behavior of 100 hospitalized

children is described. Fifty-four children showed a subdued type of behavior under the drug. Twenty-one failed to respond, 19 showed psychomotor stimulation, 6 responded by improved scholastic performance without other behavior changes, and 7 became clinically worse. The suggestion is made that this drug influences the behavior of children by altering their emotional reaction to irritating situations. No serious side effects were noted.

42. Bradley, C., and Green, E.: Psychometric performance of children receiving amphetamine (Benzedrine) sulfate. *Am. J. Psychiat.*, 97:388-394, 1940.

The effect of amphetamine sulfate upon the intelligence scores of 21 children is noted. Performance on the revised Stanford-Binet scale and a battery of psychomotor tests was not significantly affected. It is suggested that amphetamine sulfate may result in an apparent intellectual improvement in certain situations by its effect on the emotional attitude of the individual toward his task.

43. Braun, M.: Pacatal. *Am. J. Psychiat.*, 113:838-839, 1957.
44. Cares, R. M., Asrican, E., Fenichel, M., Sack, P., and Severino, J.: Therapeutic and toxic effects of chlorpromazine among 3,014 hospitalized cases. *Am. J. Psychiat.*, 114:318-327, 1957.
45. Carter, C. H.: The effects of reserpine and methyl-phenidylacetate (Ritalin) in mental defectives, spastics, and epileptics. *Psychiat. Res. Rep.*, 4:44-48, 1956.

This paper reports the effects of reserpine and methylphenidate used separately and together on the behavior, sociability, general learning, and functional IQ of 223 children and adolescents. Total improvement and improvement in specific categories are tabulated by diagnosis. Over-all improvement following therapy with both drugs combined was excellent in 34 patients, good in 144, and poor in 37. No side effects of methylphenidate were observed, and the side effects of reserpine (nasal congestion, increased gastrointestinal activity) were minimal.

46. Carter, C. H., and Maley, M. C.: Chlorpromazine therapy in children at the Florida Farm Colony. *Am. J. M. Sc.*, 33:131-136, 1957.

One hundred and fifty-three children diagnosed as mental defectives, prepsychotics, epileptics, or spastics were treated with chlorpromazine for at least six months and in some cases for a year or longer. Improvement was evaluated by degree of relief of symptoms and degree of response to training. Results were considered excellent in 52%, good in 25%, fair in 12%,

and poor in 10%. Response to therapy is tabulated and discussed in terms of diagnosis. Drowsiness was the only side effect. Observations are also made on the effects of reserpine combined with mephenesin or glutamic acid in relaxing skeletal muscles.

47. Cleveland, W. W., and Smith, G. F.: Complications following the use of prochlorperazine (Compazine) as an antiemetic. *A.M.A. J. Dis. Child.*, 96:284-287, 1958.

Four cases are presented which appear to represent side effects of prochlorperazine administration as manifested by spasm of voluntary muscles, particularly of the neck, face, tongue, and spine. Although without sequelae, such reactions may constitute a problem in diagnosis.

48. Clothier, F.: The present status of the use of newer drugs in child psychiatry. Paper read at American Orthopsychiatric Association, New York, March, 1958.

The author reports the trial use—over the course of a year and a half—of reserpine in 42 disturbed children in a residential diagnostic study home. During this period some of the children were transferred to foster homes. Medical examinations, laboratory and EEG studies, and observations by teachers, matrons, and counselors were carried out before and at intervals during drug therapy. IQ and normality of EEG are considered in evaluating response to drug.

49. Craft, M.: Tranquillizers in mental deficiency: hydroxyzine. *J. Ment. Sc.*, 103:855-857, 1957.

Hydroxyzine was compared with a placebo in a double-blind investigation carried out with 10 adults and 13 children, all of whom were institutionalized mental defectives who were aggressive and destructive. The majority were idiots; eight were grand mal epileptics. No significant difference appeared in a rating scale assessing activity, aggression, and social behavior, nor was there any significant difference between test-retest results on the Terman-Merrill scale. No toxic reactions occurred.

50. Cutler, M., Little, J. W., and Strauss, A. A.: Effect of Benzedrine on mentally deficient children. *Am. J. Ment. Deficiency*, 45:59-65, 1940.

Medication by small doses of amphetamine sulfate did not show much effect on mental reactions of mentally retarded children as measured by several psychometric tests. There were no changes in behavior, either favorable or unfavorable.

51. Cutts, K. K., and Jasper, H. H.: Effect of Benzedrine sulfate and

phenobarbital on behavior problem children with abnormal electroencephalograms. *Arch. Neurol. & Psychiat.*, 41:1138-1145, 1939.

The effect of amphetamine sulfate and phenobarbital was studied on 12 behavior problem children with abnormal electroencephalograms. About half of these patients showed marked improvement in behavior with amphetamine therapy. Phenobarbital was found to be contraindicated in the treatment of these children.

52. Denber, H. C. B., and Merlis, S.: Studies on mescaline. VI. Therapeutic aspects of the mescaline-chlorpromazine combination. *J. Nerv. & Ment. Dis.*, 122:463-469, 1955.
53. Denhoff, E., and Holden, R. H.: The effectiveness of chlorpromazine (Thorazine) with cerebral palsied children. *J. Pediat.*, 47:328-332, 1955.

This paper reports the results of an evaluation of the physical and behavioral effects of chlorpromazine in 18 cerebral palsied children, each of whom served as his own control. Improvement was rated by occupational and physical therapists and by the speech therapists and nursery school teacher. Improvement occurred in 50% of the children when on chlorpromazine, a significantly greater improvement than occurred when they were on placebo. No toxic effects were noted.

54. Dice, N., Bagchi, B. K., and Waggoner, R. W.: Investigation of effects of intravenous reserpine in disturbed psychotic and brain-damaged patients. *J. Nerv. & Ment. Dis.*, 122:472-478, 1955.

One of the four investigations reported in this paper was a study of the effects of reserpine on 10 hospitalized, brain-damaged children, 8 to 15 years old, who were compared with 10 untreated children in another institution. Drug effects were evaluated by comparing pre- and postdrug psychiatric, physical, and neurological examinations and psychological test scores (Bender-Gestalt and three Wechsler subtests). Results are fully discussed. Five drug-treated children improved slightly and five remained unimproved. In general, side effects, particularly nausea and vomiting, were more marked in children than in adults. Most of the children showed a rise in blood pressure and postural hypotension after injection of reserpine. The effects of intravenously and orally administered reserpine are compared.

55. Durling, D., Esen, F. M., and Mautner, H.: Central autonomic

regulation and mental retardation. *Ann. Paediatrici.*, 187:467-470, 1956.

Fourteen mentally retarded nonpsychotic boys aged 8 to 14 were treated for eight weeks with chlorpromazine. A control group of nine children received no medication. Some behavioral improvement occurred in the drug-treated group. There was an average gain of 10.1 points in IQ in the drug-treated group as compared to a gain of 7.6 points in the controls. The correlation between drug effects and response to the Mecholyl test is discussed.

56. Effron, A. S., and Freedman, A. M.: The treatment of behavior disorders in children with Benadryl. *J. Pediat.*, 42:261-266, 1953.

A clinical trial of diphenhydramine was carried out with 44 children, ranging in age from 6 to 12, who had various types of psychiatric disturbances. The drug was given in increasing doses for four weeks. Behavior ratings and EEG's were made, the Bender-Gestalt given, and Goodenough and free drawings were made before and during drug therapy. Results are tabulated by diagnosis and age. Sixty-one per cent showed some improvement. The children with primary behavior disorders were most benefited. No toxic symptoms were seen.

57. Eiber, H. B.: Chlorpromazine (Thorazine)-rauwolfia combination in psychiatry. *A.M.A. Arch. Neurol. & Psychiat.*, 74:36-39, 1955.

58. Esen, F. M., and Durling, D.: Thorazine in the treatment of mentally retarded children. *Arch. Pediat.*, 73:168-173, 1956.

The effects of chlorpromazine were investigated in 14 hyperactive, mentally retarded boys. A control group of nine boys received no medication. All children were tested with the Wechsler-Intelligence Scale for Children before and at the close of treatment. Behavioral improvement was evaluated by teachers' and matrons' reports. In the drug-treated group, marked improvement occurred in four children, and the majority showed moderate improvement in school work and in general behavior. IQ in the drug group increased an average of 10.1 points; in the control group it increased an average of 7.6 points. Drowsiness and weight gain were each seen in three children; moderate hypersomnia was seen in the majority. One child developed pneumonia while on drug treatment, and three had pyrexia, but there is no suggestion that these disorders were related to drug therapy.

59. Fabing, H. D., and Hawkins, J. R.: A year's experience with Frenquel in clinical and experimental schizophrenic psychoses. *Dis. Nerv. System*, 16:329-338, 1955.

60. Fabing, H. D., Hawkins, J. R., and Moulton, J. A. L.: Clinical studies on α -(2-piperidyl) benzhydrol hydrochloride, a new antidepressant drug. *Am. J. Psychiat.*, 111:832-837, 1955.
61. Fabisch, W.: Chlorpromazine and epilepsy. *Lancet*, 1:1277, 1955.
62. Fazekas, J. F., Shea, J. G., Ehrmantraut, W. R., and Alman, R. W.: Convulsant action of phenothiazine derivatives. *J.A.M.A.*, 165:1241-1245, 1957.
63. Fischer, E.: Reserpine (Serpasil) in mental deficiency practice. *J. Ment. Sc.*, 102:542-545, 1956.

To assess reserpine's effectiveness in controlling the deviant behavior of low and medium grade mental defectives, the drug was tried, with a period of placebo between two drug trials, on 22 of the most inaccessible, noisy, aggressive patients at an institution. Seven were epileptic and 10 had psychotic traits. The age range was 11 to 57 years. Clinical observation rated 14 much improved, 6 improved, and 2 unchanged. The frequency and severity of seizures were reduced in three epileptics, and the severity only in the other four. No toxic effects were seen. One patient developed an allergic rash. Two case histories are given.

64. Flaherty, J. A.: Effect of chlorpromazine medication on children with severe emotional disturbance. *Delaware State M. J.*, 27:180-184, 1955.

The author reports a six-month trial of chlorpromazine in 16 hospitalized children who were hyperactive, intractable, hostile, and aggressive. The age range was 6 to 15 years. Definite improvement occurred in 12; there was not much change in 2, and no change in 2. The only observed side effects were drowsiness during the first few days, fatigue, and one case of pseudo-parkinsonism. Two illustrative case histories are given.

65. Freed, H.: Some preliminary observations on the use of Vesprin in children and adults. *Monogr. Ther.*, 2:197-202, 1957.

The first part of this paper reports the treatment of 12 children—7 with primary behavior disorder, 4 with reading disability and neurotic traits, and 1 with severe obsessive-compulsive neurosis—with trifluopromazine. Some improvement occurred in 11. Observations are tabulated by age, sex, diagnosis, dosage, response, side effects (essentially none), and response to other tranquilizers.

66. Freed, H.: The tranquilizing drugs and the school child. *Am. Pract.*, 8:377-380, 1957.

The author discusses the pros and cons of the use of tranquilizers in

the treatment of disturbed school children, reviews some of the literature, and summarizes 2½-year follow-up data on hyperkinetic emotionally disturbed children treated 4 to 16 months in a child psychiatry clinic. He feels that the tranquilizers have therapeutic value and can be used as adjuvants in treating emotionally disturbed children with normal intelligence when psychotherapy with the child and both parents cannot be used, and in emotionally disturbed mentally deficient children with whom psychotherapy is impossible. A combination of psychotherapy and drug therapy is recommended as a practical procedure.

67. Freed, H.: The use of tranquilizers in a child psychiatry clinic. Paper read at American Orthopsychiatric Association, New York, March, 1958.

The author summarizes a controlled study of the effects of chlorpromazine on 60 hyperkinetic, emotionally disturbed boys with reading disabilities. Of the four matched groups of children, one received placebo, one placebo plus reading instruction, one chlorpromazine, and one chlorpromazine plus reading instruction. Statistical analysis of the findings indicated that chlorpromazine was a useful adjunct in these cases. Additional observations and comments on the use of tranquilizers in children are summarized.

68. Freed, H., and Peifer, C. A., Jr.: Some considerations on the use of chlorpromazine in a child psychiatry clinic. *J. Clin. & Exper. Psychopath.*, 17:165-169, 1956.

This paper brings up to date an earlier report by the same authors. Seventy children, ranging in age from 3 to 15 years, were treated with chlorpromazine for hostility or tension. Improvement occurred in three out of four, and few became worse. It is noted that two children with uncontrolled epilepsy were controlled with chlorpromazine combined with anticonvulsants. Dosages are reported. No side effects occurred. The authors suggest various reasons for the absence of parkinsonism as a side effect in children.

69. Freed, H., and Peifer, C. A.: Treatment of hyperkinetic emotionally disturbed children with prolonged administration of chlorpromazine. *Am. J. Psychiat.*, 113:22-26, 1956.

This paper reports an own-placebo-control investigation of the effects of chlorpromazine in 25 hyperactive children (primary behavior disorders, psychoneurotics, ambulatory schizophrenics, and reactive behavior disorders with organic disease). Improvement, as evaluated by behavioral changes, school achievement, and pre- and posttreatment battery of psychological tests (IQ, performance, and projective), occurred in 21. Marked behavioral improvement occurred in 18, with decreased hyperactivity as the outstanding phenomenon. Learning also seemed to be facilitated.

Drowsiness and nightmares were the only side effects, and they did not require withdrawal of the drug. Two case summaries are presented.

In the discussion following the paper, Thaddeus P. Krush summarizes his and Brian Hunt's study of 58 children being treated with chlorpromazine. In addition to drowsiness, they have observed various side effects in a few cases: urticarial reaction, mild edema, reactivation and increase in seizures.

70. Freedman, A. M.: Drug therapy in behavior disorders. *Pediat. Clin. N. Amer.*, 5:573-594, 1958.

This is a review of the literature, citing 63 references.

71. Freedman, A. M.: Treatment of autistic schizophrenic children with Marsilid. *J. Clin. & Exper. Psychopath.*, 19:Suppl. 1, pp. 138-145, 1958.

A clinical trial with iproniazid is reported for 14 children aged 4 to 10 whose diagnosis was childhood schizophrenia of the autistic type. All received other forms of therapy as well as iproniazid. Evaluation was based on staff observations, reports from parents, colleagues, and school staff (special school for schizophrenic children), and ratings of 11 categories of symptoms and behavior. The procedures, dosage, and results are fully discussed. Seven definitely improved, three improved slightly, and four failed to improve.

72. Freedman, A. M., Effron, A. S., and Bender, L.: Pharmacotherapy in children with psychiatric illness. *J. Nerv. & Ment. Dis.*, 122:479-486, 1955.

The authors report a double-blind study of the effects of various drugs (diphenhydramine, chlorpromazine, mephenesin, reserpine, and others) and a placebo on a group of 195 hospitalized children (schizophrenics, organic cases, and primary behavior disorders). Psychiatrists, nurses, psychologists, teachers, and recreational instructors rated each child on eight categories of behavior before and during drug therapy. EEG's were made and psychological tests given where possible. Results with each medication are tabulated and discussed in terms of diagnosis and change shown in the rated categories of behavior. Differences between placebo and each drug are statistically analyzed for each category. Side effects, none of which was serious, are discussed by drug.

73. Freedman, A. M., Kremer, M. W., Robertiello, R. C., and Effron, A. S.: The treatment of behavior disorders in children with Tolserol. *J. Pediat.*, 47:369-372, 1955.

The effects of mephenesin were investigated in 22 continuously observed

children (schizophrenics, organics, primary behavior disorders) between the ages of 6 and 12. Staff rated each child on improvement in seven categories (motor activity, anxiety, relationship problems with other children and with adults, affect, etc.). Improvement figures are tabulated by category of behavior, diagnosis, age, and IQ. Definite improvement occurred in all children with the diagnosis of organic behavior disorder. No side effects are reported.

74. Garrison, M., Jr.: Use of chlorpromazine and reserpine in mentally defective children. *Train. Sch. Bull.*, 53:55-63, 1956.

75. Gatski, R. L.: Chlorpromazine in the treatment of emotionally maladjusted children. *J.A.M.A.*, 157:1298-1300, 1955.

The effects of chlorpromazine were investigated in nine acutely disturbed, chronically acting-out boys, aged 6 to 13. The drug-treated group was compared to untreated children. Improvement occurred in all children on chlorpromazine, and they were able to establish rapport with the therapist. No side effects were observed.

76. Gerard, D. L., Weisselberger, D., and Kritz, D.: Reserpine in the post-withdrawal rehabilitation of adolescent opiate addicts. *A.M.A. Arch. Neurol. & Psychiat.*, 76:106-108, 1956.

A controlled study of the effects of reserpine was carried out with 27 adolescent opium addicts one month after withdrawal of opiates had been completed. Only two subjects in the experimental group improved, none in the control group. Four were not affected by reserpine; 10 were not affected by placebo. Eight on reserpine became progressively worse, two of whom developed acute psychotic states; three on placebo changed for the worse, one becoming psychotic and two increasingly depressed.

77. Geyer, H. W.: Thorazine (chlorpromazine) and Serpasil therapy in hyperactive patient of low mentality. *Delaware State M. J.*, 27:187-189, 1955.

The author presents the case report of an 11-year-old mental defective who was hyperactive, destructive, and autocombative. A program of chlorpromazine combined with reserpine resulted in marked improvement in behavior. No side effects were observed.

78. Geyer, H. W.: Response to Thorazine (chlorpromazine) administration in hyperkinetic mongolism. *Delaware State M. J.*, 28:189-190, 1956.

The author presents the case history of a nine-year-old hyperkinetic, retarded, mongoloid boy. Immediate, dramatic improvement occurred in

his behavior within three hours of the first administration of chlorpromazine. The drug was continued for four months, and the child had continued to maintain his improvement four months after the end of treatment.

79. Gillette, H. E.: Relaxant effects of meprobamate in disabilities resulting from musculoskeletal and central nervous system disorders. *Int. Rec. Med.*, 169:453-468, 1956.

Of the 28 cases of CNS disturbances treated with meprobamate and physiotherapy, 17 were children and adolescents. Age, diagnosis, duration of condition, dosage, duration of therapy, clinical response, side effects, and special remarks are tabulated for each patient. Some degree of improvement occurred in 76% of the group with CNS lesions after meprobamate was added to physical therapy. Except for one case of vomiting and somnolence, drowsiness was the only side effect. Brief case reports are given for three children.

80. Gillette, H. E.: The effect of meprobamate on cerebral palsy. *Ann. New York Acad. Sc.*, 67:859-872, 1957.

This paper reports the effects of meprobamate on muscle tone, hyperactivity, emotional control, and athetosis in cerebral palsy patients (5 adults and 48 children). Electromyographic studies were made before and during treatment. The drug favorably affected muscle tone and in certain cases had a tranquilizing action. Effects on symptoms are presented in a number of figures. Four case histories are cited.

81. Gillie, A. K.: The use of Pacatal in low-grade mental defectives. *J. Ment. Sc.*, 103:402-405, 1957.

This paper reports an own-control, double-blind study of the effects of mepazine (as compared to placebo and no drug) in 30 mental defectives (age range of 8 to 41 years, IQ of 40 or less) who were hyperkinetic, destructive, noisy, incontinent, aggressive and violent, and had dirty feeding habits. Changes in symptoms were the evaluative criteria. The drug seemed to have limited value except in epileptics, in 50% of whom slight improvement occurred. The author suggests that mepazine may potentiate the sedative effect of anticonvulsants. Side effects were dryness of the mouth, pyrexia, anorexia, and vomiting. Four subjects first showed symptoms of anorexia and vomiting one to two weeks after stopping the drug.

82. Ginn, S. A., and Hohman, L. B.: The use of dextro-amphetamine in severe behavior problems of children. *South. M. J.*, 46:1124-1127, 1953.

In organic-like behavior disturbances of children, d-amphetamine favorably changes disturbing behavior patterns. Normal childhood adjustment

frequently results. In a series of 34 followed-up cases, improvement was noted in 70%.

83. Haq, S. M., and Smyth, V. O. G.: Preliminary observations on the use of Largactil in psychiatry. *M. J. Malaya*, 9:205-211, 1955.

84. Harris, R. D., and Rowley, E. H.: Reserpine in cerebral palsy. *J. Pediat.*, 49:398-400, 1956.

Following a pilot study of 27 children, a controlled investigation of reserpine was begun on 42 cerebral palsied children. Evaluation of improvement was based on clinical observation. The Wechsler-Bellevue Psychological Rating Test (*sic*) was also given. Improvement, which is tabulated by diagnosis, occurred in 22. Reserpine improved cooperation, served as a tranquilizer in emotional states, allayed tension in tension athetosis, and reduced tremor in tremor athetoids. Side effects included stuffy nose, slight reduction in cardiac rate but no significant change in blood pressure, urticaria, and drowsiness which seemed to be secondary to a more relaxed state.

85. Horenstein, S.: Reserpine and chlorpromazine in hyperactive mental defectives. *Am. J. Ment. Deficiency*, 61:525-529, 1957.

A seven-month study was carried out to evaluate the effect of reserpine and chlorpromazine in a group of 36 hyperactive mental defectives. Both drugs were found to be beneficial in curbing hyperactivity in a majority of cases. The possible role of the brain stem in regulating motor activity and its relationship to hyperkinetic phenomena is mentioned.

86. Hunt, B. R., Frank, T., and Krush, T. P.: Chlorpromazine in the treatment of severe emotional disorders of children. *A.M.A. J. Dis. Child.*, 91:268-277, 1956.

Following a pilot study of 11 children, a controlled, double-blind investigation of the effects of chlorpromazine was carried out with 47 children (schizophrenics, behavior disorders, patients with extensive brain damage and secondary severe behavior disorders). Improvement was evaluated from weekly reports from counselors, teachers, occupational therapists, and psychiatrists. Altogether, 44 showed some degree of improvement, 5 were unchanged, and 5 became worse. Results are tabulated and discussed in terms of diagnosis and chronicity of illness. Side effects included edema, drowsiness, urticaria, and a mild parkinsonism. Illustrative case histories are given.

87. Joseph, R., and Alsion, F.: Premiers résultats de l'hibernation chez le nourrisson à l'hôpital Saint-Vincent de Paul. *J.A.M.A.*, 156:1540 (Abstract), 1954.

It is reported that 17 babies were treated with several drugs (chlorpromazine, promethazine, meperidine, phenobarbital) for hyperthermia; nervous signs such as convulsions, excitation or coma; and vascular collapse, with cyanosis, absence of pulse, or hypotension; three were put in hibernation for suffocating dyspnea. Good results were obtained in seven cases, in general those in which intervention was made early in the course of the disease.

88. Kanner, L., and Eisenberg, L.: Child psychiatry; mental deficiency. *Am. J. Psychiat.*, 113:617-622, 1957.

In this review of progress in 1956, the authors cite several papers on the use of drugs in child psychiatry and in mental deficiency.

89. Kidney, W.: Largactil in neonatal disorders. *Irish J. M. Sc.*, 6: 413-418, 1955.

The author reviews his own experiences and other investigators' published reports of the use of chlorpromazine and hibernation in treating infants with various disorders. He describes the types of cases, dosages, route of administration, action, and results, which were exceptionally good in 38 infants suffering from vomiting due to various causes. Comments made by several discussants are appended.

90. Kinross-Wright, V.: Chlorpromazine and reserpine in the treatment of psychoses. *Ann. New York Acad. Sc.*, 61:174-182, 1955.
91. Kirk, D. L., and Bauer, A. M.: Effects of reserpine (Serpasil) on emotionally maladjusted high grade mental retardates. *Am. J. Ment. Deficiency*, 60:779-784, 1956.

A double-blind study with reserpine was carried out with 60 institutionalized mental defectives who ranged in age from 8 to 28 years. The Rorschach and the Stanford-Binet were given before and after drug therapy. Medical examinations and behavior and adjustment ratings were made before and during therapy. Results of questionnaire scores, psychometric assessments, Rorschach tests, and teachers' reports are given. No improvement was noted in the majority of the drug-treated group. In general, side effects were mild except for the occurrence of an acute psychotic episode in one boy.

92. Kline, N. S., and Stanley, A. M.: Use of reserpine in a neuro-psychiatric hospital. *Ann. New York Acad. Sc.*, 61:85-91, 1955.
93. Kugelmass, I. N.: Psychochemotherapy of mental deficiency in children. *Int. Rec. Med.*, 169:323-338, 1956.

The author reports an investigation of the therapeutic value of 10 drugs in alleviating 25 single symptoms in 240 retarded children with various

types of behavior disturbances. The effectiveness of the 10 drugs is compared for six types of disorder. The effects and dosages of each drug are discussed, and the underlying basis of various symptoms is considered.

94. Lambros, V. S.: The use of reserpine in certain neurological disorders: organic convulsive states, enuresis, and head injuries. *Ann. New York Acad. Sc.*, 61:211-214, 1955.

95. Lehman, E., Haber, J., and Lesser, S. R.: The use of reserpine in autistic children. *J. Nerv. & Ment. Dis.*, 125:351-356, 1957.

The effects of reserpine were investigated in nine autistic children ranging in age from 3½ to 9 years. Results were evaluated by a psychiatric rating scale and by observation. Dosages, side effects, toxic symptoms, and withdrawal symptoms are reported and discussed. The authors report that some degree of tranquilization occurred in all nine children.

96. Leon, C. A.: The use of Thorazine as an adjunct in the treatment of schizophrenia. *Bull. Tulane M. Fac.*, 14:17-28, 1954.

97. Leslie, G.: Rauwolfia serpentina in the treatment of psoriasis. *Monogr. Ther.*, 1:29-32, 1956.

98. Lewis, L. F. E.: The use of chlorpromazine and of Serpasil in the treatment of psychotic patients. *Caribbean M. J.*, 18:51-66, 1956.

99. Levy, S.: The use of intravenous Frenquel in the treatment of acute psychotic and acute confusional states. Paper read at Western Divisional Meeting, American Psychiatric Association, Los Angeles, November, 1957.

100. Lindsley, D. B., and Henry, C. E.: The effect of drugs on behavior and the electroencephalograms of children with behavior disorders. *Psychosom. Med.*, 4:140-149, 1942.

Electroencephalograms and behavior ratings of 13 behavior problem children were studied during a six-week interval involving control periods without medication and periods of medication including amphetamine, phenobarbital, and diphenylhydantoin.

101. Litchfield, H. R.: Clinical evaluation of meprobamate in disturbed and prepsychotic children. *Ann. New York Acad. Sc.*, 67:828-831, 1957.

The author reports the use of meprobamate in treating 28 children (age range from 2 months to 16 years). Symptoms included restlessness,

irritability, sleeplessness, overactiveness, destructiveness, unresponsiveness to home discipline, tension, and emotional disturbance. Results are discussed in terms of age group and symptoms. A placebo control study was carried out with 16 children from comparable age groups. Drowsiness was the only side effect of meprobamate, and it occurred rarely.

102. Livingston, S.: Drug therapy for childhood epilepsy. *J. Chron. Dis.*, 6:46-80, 1957.

The classification of epileptic seizures used at the Johns Hopkins Epilepsy Clinic is presented. The various anticonvulsant drugs are discussed in detail: available preparations, dosage, indications for use, and untoward reactions.

103. Livingston, S., Kadji, L., and Bridge, E. M.: The use of Benzedrine and Dexedrine sulfate in the treatment of epilepsy. *J. Pediat.*, 32:490-494, 1948.

Eighty-five epileptic patients, mostly children, were treated with amphetamine or d-amphetamine sulfate; the seizures were controlled in 38% and markedly or moderately improved in 20%.

104. Livingston, S., and Pauli, L.: Meprobamate in the treatment of epilepsy of children. *A.M.A. Arch. Dis. Childhood*, 94:277-281, 1957.

One hundred and twenty-eight epileptic children, 59% of whom also manifested hyperactive behavior disorders, were treated with meprobamate for periods ranging from nine months to two years. Some were given anticonvulsants along with meprobamate. Behavior disorders were alleviated in 42% in whom such disorders were present, and meprobamate controlled or reduced minor motor seizures in 13 of 41 patients. Major motor, petit mal, and psychomotor seizures were not significantly relieved. No side effects occurred except drowsiness in a few patients, and diarrhea in one patient each time the drug was given.

105. Low, N. L., and Myers, G. G.: Suvren in brain-injured children. *J. Pediat.*, 52:259-263, 1958.

Forty hyperkinetic children with patterns of organic brain damage were treated with captodiamine. Dosage varied from 100 to 240 mg. daily for periods of 3 to 17 months. Twenty-three patients showed striking improvement in action and behavior. No significant side effects or toxic reactions were noted. It was felt that captodiamine is a safe and useful chemotherapeutic agent in the treatment of hyperactive children with brain damage.

106. Luhby, A., Cooperman, J. M., and Halkins, C. R.: Effect of

Marsilid on weight and growth of children. *J. Clin. & Exper. Psychopath.*, 19:Suppl. 1, pp. 132-137, 1958.

This study indicates that iproniazid, given at a dosage level of 2 mg/kg/day for nine weeks, does not produce a significant increase in appetite, weight, or height in undersized but otherwise normal children six to nine years of age.

107. MacGregor, J. M.: Largactil, a new psychomotor brake. *South African J. Clin. Sc.*, 5:228-243, 1954.

108. Mecham, M. J., Stromsta, C., and Soderberg, G.: Effects of Tolserol on the speech errors of mentally defective children. *Am. J. Phys. Med.*, 34:535-536, 1955.

An experimental study was carried out with 22 mental defectives with speech defects to test the hypothesis that there is no significant difference in the number of speech errors of mentally defective patients with increased relaxation resulting from the application of mephenesin. Speech recordings were made before medication, after placebo, and after drug. The difference between the drug and no-drug conditions was not significant.

109. Miksztal, M. W.: Chlorpromazine (Thorazine) and reserpine in residential treatment of neuropsychiatric disorders in children. *J. Nerv. & Ment. Dis.*, 123:477-479, 1956.

Seventy-four 6-to-15-year-old children (schizophrenics, chronic brain syndromes, adjustment reactions, mental defectives with psychotic reaction, or personality disorders) were treated with either reserpine or chlorpromazine. Daily and weekly observations and evaluations were made of each child, and clinical and laboratory tests were made regularly. Several tables present information on diagnosis, dosage, duration of treatment, and degree of improvement. Marked or moderate improvement occurred in 65 to 81%, depending on the diagnosis and the drug used. Drug effects on symptoms are also discussed. Side reactions included elevated leukocytes and eosinophilic cells and a transient mild diarrhea. In 18 patients on reserpine, a minimal asymptomatic lowering of the diastolic blood pressure occurred.

110. Millen, F. J.: Miltown—clinical experiences in neuropsychiatric office use. *Wisconsin M. J.*, 56:198-201, 1957.

111. Molitch, M., and Eccles, A. K.: The effect of Benzedrine sulfate on the intelligence scores of children. *Am. J. Psychiat.*, 94:587-590, 1937.

Ninety-three boys between the ages of 11 and 17, and of varying mental

levels, were tested at intervals before and after a placebo or amphetamine sulfate was ingested. Both groups improved their scores, the children tested after taking amphetamine exhibiting a greater improvement than those taking a placebo.

112. Molitch, M., and Poliakoff, S.: The effect of Benzedrine sulfate on enuresis. *Arch. Pediat.*, 54:499-501, 1937.

Eight of 22 bed-wetters were relieved of their enuresis with a placebo. Of the 14 boys who failed to respond to placebos, 12 (86%) were entirely relieved of their enuresis when given increasing small doses of amphetamine. All 22 reverted to bed-wetting within two weeks after they were taken off both placebo and amphetamine. No serious side effects were noted.

113. Molitch, M., and Sullivan, J. P.: The effect of Benzedrine sulfate on children taking the New Stanford Achievement Test. *Am. J. Orthopsychiat.*, 7:519-522, 1937.

Amphetamine sulfate improved the total (average) scores of boys as revealed by the New Stanford Achievement Test. There were no unfavorable reactions of any serious consequence, especially with smaller doses.

114. Morris, J. V., MacGillivray, R. C., and Mathieson, C. M.: The results of the experimental administration of amphetamine sulphate in oligophrenia. *J. Ment. Sc.*, 101:131-140, 1955.

In a controlled study of the effects of amphetamine on mental defectives, the drug was not found to significantly increase intelligence, learning capacity, speed and accuracy of voluntary attention, fluency, or memory. There was no evidence that amphetamine facilitates CNS action to a point where the mentally handicapped can benefit from educational training.

115. Morton, H. G., and Warson, S. R.: Control study on reserpine in small group of children with neurologic disorders. *J. Florida M. A.*, 43:786, 1957.

This paper reports an own-control, double-blind study of the effects of reserpine as an adjuvant in the treatment and management of children with neurological disease. Of the 29 patients studied, 16 were children. Teachers and physical therapists rated the children on coordination, relaxation, strength, alertness, attention span, social behavior, and psychological reactions. Results were negative and are not cited in detail.

116. Moskowitz, H.: Benzedrine therapy for the mentally handicapped. *Am. J. Ment. Deficiency*, 45:540-543, 1941.

In selected cases of uncomplicated oligophrenia, prolonged administration of amphetamine sulfate raises the ability of the central nervous system

of the mentally handicapped to the point where educational training can be utilized, resulting in greater performance ability. The selection of these cases may be correlated with somatic factors such as body measurements and response to adrenalin injection.

117. Moyer, J. H., Kinross-Wright, V., and Finney, R. M.: Chlorpromazine as a therapeutic agent in clinical medicine. *A.M.A. Arch. Intern. Med.*, 95:202-218, 1955.

118. Nathan, L. A., and Andelman, M. B.: The use of a tranquilizer in the management of behavior problems in a private pediatric practice. *Illinois M. J.*, 112:171-174, 1957.

Report of a study carried out in a private pediatric practice in which 58 children received hydroxyzine syrup for various symptoms of abnormal behavior. Response to the medication was individualized and a large majority of the patients showed striking improvement. No adverse side reactions were noted.

119. Nichamin, S. J.: Chlorpromazine in the treatment of mild behavior disturbances. *J. Michigan M. Soc.*, 55:1469-1471, 1956.

The author reports the use of chlorpromazine in treating 22 children with minor behavior disorders. Drug effects were determined by observations of the children and interviews with them and with their parents. Response was good in 14, poor in 8. The only side reaction was transient drowsiness in one case. Brief case histories are given for the 14 children who responded favorably.

120. Nichtern, S.: Neurological agents in child psychiatry. *Dis. Nerv. System*, 18:72-75, 1957.

The author reviews recent progress and development in the use of chemotherapeutic agents in children, and summarizes several studies in that area. The paper is discussed by George A. Jervis.

121. Nicolaou, G. T., and Kline, N. S.: Reserpine in the treatment of disturbed adolescents. *Psychiat. Res. Rep.*, 1:122-132, 1955.

Reserpine was found to be a useful implement in the psychotherapy of a group of disturbed, hospitalized male adolescents ranging between 11 and 15 years of age. Results and side effects are compared between low and high dosages of the drug.

122. Oettinger, L., Jr.: Meratran; preliminary report of a new drug for the treatment of behavior disorders in children. *Dis. Nerv. System*, 16:299-302, 1955.

Pipradrol was tried in 47 outpatient children with behavior disorders. The age range was 5 to 15 years. With few exceptions, the children were observed for three months or longer. The Bender-Gestalt and Goodenough Draw-A-Man tests were given before and during medication and evaluated for improvement. Other improvement figures were based on reports from family and school and on observation. Some improvement occurred in 55%; approximately 20% became worse; and 25% showed no change. No correlation was found between results and EEG findings. No side effects were reported.

123. Oettinger, L., Jr.: The use of deanol in the treatment of disorders of behavior in children. *J. Pediat.*, 53:671-675, 1958.

Deanol was used in the treatment of behavior disorders in 108 non-epileptic and 17 epileptic children. In 68% of the nonepileptic group, this agent proved beneficial in that the children came to act in a more socially accepted way, and learning in school improved. In the epileptic group, deanol was not as beneficial as amphetamine and related drugs. No toxicity or significant side effects were noted.

124. O'Sullivan, C. J.: Myanesin in tension states. *J. Irish M. A.*, 30:167-169, 1955.

125. Pasamanick, B.: Anticonvulsant drug therapy of behavior problem children with abnormal electroencephalograms. *A.M.A. Arch. Neurol. & Psychiat.*, 65:752-766, 1951.

Twenty-one boys with behavior problems, 6 to 13 years of age, with various electroencephalographic abnormalities received one or more anticonvulsant drugs, including diphenylhydantoin, mesantoin, tridione, and phenobarbital. With minor exceptions the results were uniformly disappointing in producing any significant improvement in behavior. An attempt is made to explain the psychodynamics involved in the improvement of behavior disorders under drug administration in outpatient use, and a hypothesis is offered for the rationale of amphetamine therapy in the behavior disorders.

126. Perlstein, M. A.: Use of meprobamate (Miltown) in convulsive and related disorders. *J.A.M.A.*, 161:1040-1044, 1956.

Meprobamate was administered to 130 patients (including 124 children) with nervous disorders characterized by seizures, hyperactivity, or tension form of cerebral palsy. The drug was given alone and in combination with other drugs. Patients who responded favorably to meprobamate were subsequently tried on placebos. Results are discussed in terms of diagnosis. Drowsiness was the only observed side effect; blood, skin, liver, or urinary changes were not encountered.

127. Pomeranze, J.: Preliminary observations on the use of rauwolfia in labile diabetes. *Monogr. Ther.*, 1:26-28, 1956.
128. Prouet, P. E.: Rauwolfia and amphetamine therapy in the treatment of psychosomatic complaints. *J. Louisiana M. Soc.*, 107: 114-116, 1955.
129. Ray, P. K.: The use of Rauwolfia serpentina in psychiatry. *Indian J. Neurol.*, 3:380-398, 1952.
130. Rees, E. L.: Metabolism of the schizophrenic child; etiologic hypothesis. Addendum: report of six cases treated with chlorpromazine hydrochloride. *J. Am. M. Women's A.*, 11:11-16, 1956.

Two brief case reports are given for schizophrenic boys aged 10½ and 9 who were benefited by treatment with atropine. Six case reports of severely disturbed children who were treated with chlorpromazine are given in an addendum to the paper.

131. Rettig, J. H.: Chlorpromazine for the control of psychomotor excitement in the mentally deficient; a preliminary study. *J. Nerv. & Ment. Dis.*, 122:190-194, 1955.

This paper reports the results of six months' chlorpromazine treatment of 27 highly disturbed mental defectives, 15 of whom were between the ages of 14 and 19. Results in terms of manageability of the adolescents ranged from one in whom there was no change to five in whom the results were excellent. Age, sex, IQ, diagnosis, length of institutionalization, behavior before and after chlorpromazine, and results in terms of manageability are given for each patient. The case history of a 15-year-old girl is cited. Side effects included transient drowsiness, two cases of anorexia, one case of vomiting, one severe depression, and one slight depression.

132. Rettig, J. H.: Chlorpromazine and Mysoline in the control of convulsive epilepsy in mentally deficient patients. *J. Nerv. & Ment. Dis.*, 124:607-611, 1956.
133. Rosenblum, S., Callahan, R. J., Buoniconto, P., Graham, B., and Deatrick, R. W.: The effects of tranquilizing medication (reserpine) on behavior and test performance of maladjusted, high-grade retarded children. *Am. J. Ment. Deficiency*, 62: 663-671, 1958.

A controlled double-blind study was carried out to determine the effectiveness of reserpine in 130 high-grade retarded children who were personally and socially maladjusted. Binet tests (L and M), the Chil-

children's Manifest Anxiety Scale, the Children's Anxiety Pictures, and the Gardner-Thompson Rating Scale were given pre- and postexperimentally; the Graphic Rating Scale was given weekly. There was no significant difference between drug and placebo groups, although there was a tendency toward improvement in cottage and classroom behavior in a greater percentage of the placebo group than in the drug groups.

134. Rosner, S.: The use of reserpine in neurologic surgery. *J. Int. Coll. Surgeons*, 25:480-482, 1956.
135. Sainz, A.: Chlorpromazine in psychiatric disorders. *Prescriber*, 2:14-21, 1955.
136. Sainz, A. A.: The management of side effects of chlorpromazine and reserpine. *Psychiatric Quart.*, 30:647-653, 1956.
137. Segal, L. J., and Tansley, A. E.: A clinical trial with hydroxyzine (Atarax) on a group of maladjusted educationally subnormal children. *J. Ment. Sc.*, 103:677-681, 1957.

A trial was carried out to evaluate the effects of hydroxyzine in 16 matched pairs of maladjusted, educationally subnormal children whose school performance was not up to their capacities. All were in a residential school. Improvement, as evaluated by behavior and class performance, occurred in 14 drug-treated children and in 2 children in the placebo group. In no case did leukopenia or granulopenia occur to a degree warranting interference with treatment. A transient eosinophilia and increased monocytes occurred but cleared quickly. Four very brief case reports are given.

138. Selling, L. S.: Clinical study of a new tranquilizing drug. Use of Miltown (2-methyl-2-n-propyl-1, 3-propanediol dicarbamate). *J.A.M.A.*, 157:1594-1596, 1955.
139. Settel, E.: Clinical observations on the use of hydroxyzine in anxiety-tension states and senile agitation. *Am. Pract.*, 8:1584-1588, 1957.
140. Shea, J. G., Ehrmantraut, W. R., Ticktin, H. E., Sullivan, P. D., Jr., and Fazekas, J. F.: Use of promazine in the management of medical emergencies. *Mil. Med.*, 119:221-227, 1956.
141. Sherwin, A. C., Flach, F. F., and Stokes, P. E.: Treatment of psychoses in early childhood with triiodothyronine. *Am. J. Psychiat.*, 115:166-167, 1958.

The cases of two children treated with triiodothyronine are presented.

Acute periods of anxiety and fear were present in the early stages of medication. Zinc corticotrophin combined with triiodothyronine resulted in reinforcement of the increase in contact and affective display noted with triiodothyronine alone. Hyperactivity appears to be less marked in combination than with zinc corticotrophin alone and more marked than with triiodothyronine alone.

142. Silver, A. A.: Management of children with schizophrenia. *Am. J. Psychother.*, 9:196-215, 1955.

This review includes a section on the place of drugs in the management of schizophrenic children. The uses, effects, dosages, and side effects of stimulants, anticonvulsants, antihistamines, tranquilizers, and other drugs are summarized.

143. Souder, C. L. R.: Thorazine in surgical-psychiatric emergencies. *Delaware State M. J.*, 27:191-193, 1955.

144. Sparup, K. H.: Meprobamate. *Lancet*, 2:807, 1957.

In a letter to the editor, the author summarizes a trial of meprobamate in 33 cerebral palsy patients, 29 of whom were children. Dosages are reported, and results are tabulated by diagnostic group. Meprobamate was also tried in combination with primidone, but the findings indicated that a better effect was achieved when the two drugs were given separately.

145. Sprogis, G. R., Lezdins, V., White, S. D., Ming, C., Lanning, M., Drake, M. E., and Wyckoff, G.: Comparative study on Thorazine and Serpasil in the mental defective. *Am. J. Ment. Deficiency*, 61:737-742, 1957.

The comparative effectiveness of chlorpromazine, reserpine, and placebo in reducing behavior disturbances in nonpsychotic mental defectives was investigated in 154 institutionalized mental defectives from 8 to 60 years old. Drug effects were evaluated by observations and supervisors' reports. Side effects and therapeutic results after four and eight months of treatment are tabulated and discussed, along with comments on maintenance of improvement after withdrawal of drug, and on drug effects on incidence of seizures in epileptics. Side effects of reserpine were drowsiness, allergic dermatitis, moderate hypotension, tachycardia, bradycardia. Side effects of chlorpromazine were drowsiness, loss of facial movement and hand tremors, moderate hypotension, tachycardia, lactation. During the study four patients died of intercurrent disease. One patient developed bronchopneumonia and died; autopsy findings are reported.

146. Steigman, A. J.: Newer drugs which influence behavior. *Pediatrics*, 20:732-737, 1957.

The author reviews the chemistry of the phenothiazine derivatives, reserpine, and meproamate and their uses and side effects in children.

147. Steigman, A. J., and Vallbona, C.: Experience with chlorpromazine in pediatrics. *Int. Rec. Med.*, 168:351-357, 1955.

148. Stritzler, C.: Discussion of Dr. Bleiberg's paper, "A preliminary report on a new approach to the treatment of acne vulgaris." Paper read at Hoffmann-La Roche, Inc. Symposium on the biochemical and clinical aspects of Marsilid and other monoamine oxidase inhibitors, New York, November, 1957.

149. Talbot, M. W., Jr.: The use of reserpine in irritable and hypertonic infants. *Ann. New York Acad. Sc.*, 61:188-197, 1955.

The effects of reserpine elixir were investigated in 32 infants between 7 weeks and 11½ months of age. Age, duration of symptoms, birth order, family history, sleeping patterns, and weight and rate of gain are discussed. Twenty-nine of the infants benefited from the drug, one was not helped, and in two the drug had to be stopped because of severe abdominal cramping. Other side effects included nasal stuffiness, excessive somnolence, and diarrhea. Effects of withdrawal of drug after six weeks are discussed. The 19 who reverted to pretreatment behavior were given a placebo for a week and then put back on reserpine.

150. Tarjan, G., Lowery, V. E., and Wright, S. W.: Use of chlorpromazine in two hundred seventy-eight mentally deficient patients. *A.M.A. J. Dis. Child.*, 94:294-300, 1957.

The effects of chlorpromazine on various behavior disturbances were investigated in 278 mental defectives, 141 of whom were in the 1-to-19 age group. Diagnostic groups included organics, epileptics, and psychotics. Physicians evaluated improvement by degree of change in symptoms. Results are tabulated by age group, IQ, duration of treatment, diagnosis, and symptom. Chlorpromazine was considered to be of some benefit in 70% of the patients treated. Side effects included drowsiness or lethargy, and a rapid and significant increase in seizures in 12 epileptics whose phenobarbital medication had been decreased or stopped. Two case histories of children are presented.

151. Teicher, J. D.: The new drugs and the child. *M. Times*, 85:1020-1026, 1957.

The author discusses the value of a number of drugs as aids in treating disturbed children, stressing the need for proper use of the drugs and emphasizing that suppression of symptoms does not constitute a "cure." Side effects of the drugs are also discussed.

152. Timberlake, W. H., Belmont, E. H., and Ogonik, J.: The effect of reserpine in 200 mentally retarded children. *Am. J. Ment. Deficiency*, 62:61-66, 1957.

This paper reports a double-blind investigation of the effects of reserpine or placebo on 200 mentally retarded children who had social or emotional problems. The subjects ranged in age from 3 to 63; average age was 20. Intelligence tests (Stanford-Binet, Hayes-Binet Intelligence Test for the Blind, Vineland Social Maturity Scale) were given before and during medication. Behavioral improvement occurred in 65%, but intellectual capacity was not altered. Side effects included flushing of the skin, drowsiness (which also occurred in five patients on placebo), tremor, and dizziness. Reserpine had no effect on grand mal and psychomotor automatism seizures in 31 epileptic patients.

153. Vergani, O., and Aldeghi, E.: Preliminary clinical experiments with promazine in infantile neuropsychiatry. In S. Garattini and V. Ghetti (Eds.), *Psychotropic Drugs*. Amsterdam, Elsevier Publishing Company, 1957. Pp. 558-560.

This is a report of the results of experiments with promazine in children. Thirteen of the 27 subjects were epileptic, and all of the children displayed abnormal electroencephalograms. The drug produced excellent results in 6 patients, good results in 13, moderate results in 4, and no results in 4. A brief explanation is offered for the probable mechanism of action of promazine in these patients.

154. Watkins, C.: The use of reserpine in cerebral palsy. *South. M. J.*, 49:1488-1494, 1956.

This paper reports the clinical and behavioral effects of reserpine in 15 cerebral palsied children, a number of whom had emotional problems. Four case histories are cited. A change in psychological test score is referred to in one case history, but no other mention of testing is made.

155. Weir, H. F., and Anderson, R. L.: The effects of reserpine and rauwolfia in minor disorders of adjustment in children. *Monogr. Ther.*, 1:33-39, 1956.

The authors report the results of a study of the effects of reserpine in 95 outpatient children. Results are tabulated by age, and effects on symptoms are discussed. Side effects included irritability, increase in bed-wetting in four cases, one case of severe depression, occasional drowsiness, and nasal congestion. Comparative studies were carried out with 30 children treated with rauwolfia and 14 treated with phenobarbital. The therapeutic response to rauwolfia was equal to or greater than that to reserpine. The

response to phenobarbital was inadequate in comparison to the response to tranquilizers.

156. Winkelman, N. W., Jr.: An appraisal of chlorpromazine. General principles for administration of chlorpromazine, based on experience with 1,090 patients. *Am. J. Psychiat.*, 113:961-971, 1957.

157. Wolfson, I. N.: Clinical experience with Serpasil and Thorazine in treatment of disturbed behavior of mentally retarded. *Am. J. Ment. Deficiency*, 62:276-283, 1957.

This is a preliminary report on 156 mentally retarded patients, including 20 between the ages of 5 and 10 years and others between 11 and 20, who were treated with reserpine, chlorpromazine, or both for a period of 1 to 10 months. Dosages are reported, and results and complications with each drug are tabulated.

158. Zimmerman, F. T., and Burgemeister, B. B.: Preliminary report upon the effect of reserpine on epilepsy and behavior problems in children. *Ann. New York Acad. Sc.*, 61:215-221, 1955.

The authors report an own-control, double-blind study of the use of reserpine in 87 children and adolescents, of whom 72 were epileptics and 15 mental defectives. For the epileptics, only the anticonvulsant and behavioral effects of the drug are reported. Observations and ratings of behavior of the mental defectives were made, and psychological tests (verbal and performance tests, the Rorschach, Stanford-Binet) were given, but ratings, test scores, etc., are not included in this paper. They are to be published separately. Only a summary of observed changes is given.

159. Zimmerman, F. T., and Burgemeister, B. B.: The effect of reserpine on the behavior problems of children. *New York State J. Med.*, 57:3132-3140, 1957.

This paper presents the findings after one year of a study of the effects of reserpine in an experimental group of 100 children and adolescents with severe behavior disorders, and a control series of 31 cases who were given a placebo for six months. Results were evaluated by clinical observation and psychological tests (verbal intelligence, performance, social intelligence, projective techniques, including the Rorschach) given before and during drug therapy. Results are reported in detail. About 75% of the drug-treated group improved as compared to 35 to 40% of the control group. Mild toxic reactions, which are tabulated, occurred in 7% of the drug-treated group.

SUBJECT INDEX TO REFERENCE LIST

Type of Reference

Case history, an account of one or more specific patients: 10, 23, 25, 27, 29, 32, 37, 41, 47, 63, 64, 69, 75, 77, 78, 79, 80, 82, 84, 86, 101, 105, 116, 118, 119, 123, 125, 130, 131, 137, 141, 147, 150, 151, 152, 154, 157.

Clinical report, clinical trials, without any attempt at formal controls: 3, 5, 10, 11, 14, 16, 17, 22, 23, 25, 27, 28, 32, 33, 36, 38, 40, 41, 42, 45, 46, 48, 51, 56, 64, 65, 66, 68, 71, 73, 79, 80, 82, 89, 95, 103, 104, 105, 109, 118, 119, 121, 122, 123, 125, 126, 131, 144, 145, 149, 150, 153, 154, 155, 157.

Controlled experiment, studies which contain some aspects of experimental design and in which controls were used in an attempt to answer objectively certain specific questions: 15, 49, 50, 53, 54, 55, 58, 63, 67, 69, 72, 75, 76, 81, 84, 85, 86, 91, 100, 101, 106, 108, 111, 112, 113, 114, 115, 121, 133, 137, 152, 158, 159.

General review, devoted to a number of different drugs: 4, 7, 13, 26, 39, 66, 70, 88, 93, 102, 120, 142, 146, 151.

Specific review, limited to a particular drug (or drug family): 18, 19, 37, 38, 68, 89, 116, 147.

Type of Child

"Behavior problem," all studies in which the children were categorized primarily as emotionally disturbed, behavior disorder, neurotic, etc.: 3, 5, 10, 11, 15, 22, 23, 25, 29, 32, 33, 36, 38, 40, 41, 42, 48, 51, 56, 64, 65, 66, 68, 69, 72, 73, 75, 82, 86, 100, 101, 109, 118, 119, 121, 122, 123, 149, 153, 155, 158, 159.

Infants, concerned primarily with children under the age of three: 5, 16, 33, 87, 89, 101, 149.

Mental retardation, the sample (or a significant portion) was primarily designated as mentally retarded: 3, 5, 10, 11, 15, 27, 28, 32, 33, 45, 46, 49, 50, 55, 56, 58, 63, 66, 77, 78, 81, 85, 91, 93, 109, 114, 116, 131, 133, 145, 150, 152, 157.

Neurological disorder, a significant portion of the sample had CNS impairment, e.g., cerebral palsy, epilepsy, brain damage, etc.: 5, 14, 16, 17, 25, 32, 33, 45, 46, 49, 53, 54, 56, 63, 68, 69, 72, 73, 79, 80, 84, 102, 103, 104, 105, 109, 115, 123, 125, 126, 144, 150, 152, 154, 158.

Psychosis, a significant portion of the sample was designated as psychotic (including childhood autism): 3, 5, 23, 25, 32, 56, 69, 71, 72, 73, 86, 95, 109, 121, 130, 141, 142.

Reading disorder, the sample was chosen primarily because of impaired reading ability: 67.

Speech disorder, the sample was chosen primarily because of impaired speech ability: 10, 108.

Other, includes a variety of other characteristics, e.g., enuresis, vomiting, hypothermia, undernourished children, postwithdrawal drug addicts, etc.: 27, 33, 47, 68, 69, 76, 89, 106, 111, 112, 113, 137.

Clinical Setting

Outpatient, studies in which the sample was *not* primarily residential, hospitalized, or institutionalized: 14, 22, 29, 33, 66, 68, 71, 82, 101, 102, 103, 104, 105, 115, 118, 119, 122, 123, 126, 149, 155.

Follow-up, studies in which a significant portion of the subjects were re-examined at least six months after the initial study: 27, 50, 66, 82.

Drug

Amphetamine (Benzedrine): 18, 25, 36, 37, 38, 40, 41, 42, 50, 51, 66, 100, 103, 111, 112, 113, 114, 116, 125.

- Benactyzine (Suavitil)*: 22.
- Captodiamine (Suvren)*: 105.
- Chlorpromazine (Thorazine)*: 5, 15, 17, 19, 32, 33, 46, 53, 55, 58, 64, 66, 67, 68, 69, 72, 75, 77, 78, 85, 86, 89, 109, 119, 130, 131, 145, 147, 150, 157.
- D-amphetamine (Dexedrine)*: 38, 82, 103.
- Deanol (Deaner)*: 123.
- Diphenhydramine (Benadryl)*: 5, 56, 72.
- Ectylurea (Nostyn)*: 10, 11.
- Hydroxyzine (Atarax)*: 22, 49, 118, 137.
- Iproniazid (Marsilid)*: 71, 106.
- Mepazine (Pacatal)*: 81.
- Mephenesin*: 46, 72, 73, 108.
- Meprobamate (Miltown, Equanil)*: 5, 14, 16, 17, 66, 79, 80, 101, 104, 126, 144.
- Methylphenidate (Ritalin)*: 45, 95.
- Pentylentetrazol (Metrazol)*: 28.
- Perphenazine (Trilafon)*: 29.
- Pipradrol (Meratran)*: 4, 122.
- Placebo*: 49, 50, 53, 63, 66, 67, 69, 72, 76, 81, 84, 85, 86, 91, 101, 106, 108, 111, 112, 113, 114, 115, 121, 126, 133, 137, 149, 152, 159.
- Prochlorperazine (Compazine)*: 3, 27, 47.
- Promazine (Sparine)*: 5, 17, 153.
- Reserpine and other rauwolfia alkaloids*: 5, 17, 23, 45, 46, 48, 54, 63, 66, 72, 76, 77, 84, 85, 91, 95, 109, 115, 121, 133, 145, 149, 152, 154, 155, 157, 158, 159.
- Triflupromazine (Vesprin)*: 65.
- Triiodothyronine (Cytomel, Trionine)*: 141.

Dependent Variables

Cognitive processes, explicit interest in sensory and perceptual functions: 54, 66, 67, 69, 71, 73, 114, 115, 122, 123, 133, 158, 159.

"Disturbed" behavior, an interest in over-all "improvement" in symptomatic behavior: 3, 5, 10, 11, 15, 22, 23, 25, 28, 32, 33, 36, 38, 40, 41, 45, 46, 48, 49, 51, 56, 58, 63, 64, 65, 66, 68, 71, 72, 73, 75, 76, 81, 82, 84, 85, 86, 91, 95, 101, 104, 105, 109, 118, 119, 122, 123, 125, 126, 131, 133, 144, 145, 149, 150, 152, 153, 154, 155, 157, 158.

Emotional processes, explicit interest in drive level, anxiety, etc.: 14, 22, 53, 66, 69, 71, 72, 73, 80, 85, 95, 121, 133.

Intellectual processes, explicit interest in intelligence, achievement, etc.: 15, 28, 40, 42, 45, 49, 50, 54, 55, 56, 58, 69, 73, 91, 111, 113, 114, 121, 137, 152, 159.

Medical symptoms, enuresis, vomiting, etc.: 27, 33, 69, 89, 112, 149, 157.

Neurological aspects, seizures, EEG, etc.: 10, 14, 16, 17, 32, 33, 51, 54, 63, 68, 69, 100, 103, 104, 122, 126, 144, 150, 152, 158.

Physical and motor processes, explicit interest in weight, speech, activity level, strength, etc.: 11, 28, 42, 49, 50, 53, 54, 71, 72, 79, 80, 91, 95, 106, 108, 111, 114, 115, 133, 144, 159.

Social processes, explicit interest in social relationships, including cooperation, competitiveness, etc.: 45, 49, 50, 71, 72, 73, 85, 115, 152, 159.

Type of Measure

Behavioral rating, quantified observations or ratings on relatively specific variables: 28, 45, 49, 50, 53, 54, 56, 69, 71, 72, 73, 79, 80, 85, 91, 95, 100, 115, 121, 133, 137, 145, 152, 159.

Clinical impression, unquantified observations from clinical staff, parents, teachers, and others: 3, 5, 10, 11, 14, 15, 22, 23,

25, 32, 33, 36, 38, 40, 41, 46, 48, 51, 58, 63, 64, 65, 66, 68, 69, 75, 76, 81, 82, 84, 86, 91, 95, 101, 104, 105, 109, 118, 119, 122, 123, 125, 126, 131, 144, 149, 150, 152, 153, 154, 155, 157, 158.

Experimental test, specially devised test situations, e.g., level-of-aspiration, reading facility, etc.: 42, 50, 108, 111.

Medical observation, interest in medical symptoms: 27, 33, 89, 112, 157.

Neurological measure, neurological tests and observations, e.g., seizures, EEG, etc.: 14, 16, 17, 32, 33, 51, 63, 68, 69, 100, 103, 104, 122, 126, 144, 150, 152, 158.

Objective psychological test, standard, quantified, verbal and nonverbal measures of psychological functions: 15, 40, 42, 49, 50, 54, 55, 56, 58, 66, 67, 69, 91, 111, 113, 114, 121, 123, 133, 152, 158, 159.

Physical measure, height, weight, strength, etc.: 11, 106, 111.

Projective psychological test, Rorschach, Thematic Apperception Test, Bender-Gestalt, Draw-A-Person, etc.: 54, 69, 91, 122, 123, 158, 159.

Side Effects

Neurological, convulsions, tremors, drooling, etc.: 3, 14, 29, 32, 33, 38, 41, 46, 47, 64, 69, 79, 84, 86, 95, 101, 103, 104, 119, 121, 126, 131, 145, 150, 152, 155, 159.

Physiological, vomiting, skin rash, cardiovascular changes, etc.: 5, 14, 27, 32, 33, 38, 41, 45, 54, 63, 72, 79, 81, 84, 86, 103, 104, 109, 113, 121, 131, 137, 145, 149, 152, 155, 157, 159.

INDEX

- Abood, C. G., 147
 Abrahamsen, D., 33
 Acetylcholine, 16, 165
 Activity level, 98, 107
 Adamson, W. C., 171
 Addison, R. G., 171
 Adjustment, general measure of, 100
 Adrenergic blocking action, 5, 7, 8
 Adult, mental illness in, 26
 Aggression, 56, 100
 Aghajanian, G. K., 162
 Ainsworth, M., 33
 Alcoholism, acute, 6, 8
 Aldeghe, E., 200
 Alerting reaction, 17
 Alsion, F., 188
 Allen, G. B., 101, 104
 Allen, M., 171
 Allin, T. G., Jr., 172
 Alman, R. W., 183
 Alpert, N., 147
 American Psychological Association, 141
 Amphetamine (Benzedrine), 4, 15-16, 17, 18, 44, 56
 actions of, 15
 dextro-rotatory form of, 16
 Andelman, M. B., 194
 Andermann, K., 172
 Anderson, R. L., 200
 Anesthesia, local, 12
 Anesthetics, 3
 Anhedonia, 16
 Animals, drug research in, 44, 72, 142, 148-149
 Antiadrenergic drugs, 12
 Anticholinergic drugs, 12
 Anticholinesterases, 164
 Anticonvulsants, 39
 Antidepressives (central nervous system stimulants), 4, 14-19
 clinical use of, 18-19
 trade names of, 15
 Antihistamines, 22, 39
 Antiparkinsonian medication, 9
 Antispasmodic drug, 15
 Anton-Stephens, D., 172
 Anxiety, 11, 14, 50, 60
 parents and, 108
 relief by drugs, 52, 53
 tests of, 100
 Appetite, suppression by drugs, 16
 Arellano, A. P., 172
 Ash, P., 70, 75
 Asrican, E., 179
 Asthma, 50
 Asung, C. L., 172, 173
 Ataxia, 7
 Atropine, 164
 Autism, 40
 Ayd, F. J., Jr., 173
 Azacyclonol (Frenquel), 4, 11, 13
 Azrin, N. H., 44, 46, 124

 Baer, D. M., 135
 Bagchi, B. K., 181
 Bair, H. V., 174
 Baird, H. W., 174
 Baird, H. W., III, 174
 Bakwin, H., 174
 Baldwin, A. L., 71, 75
 Barbiturates, 38, 44
 depression and, 17
 intoxication and, 17
 Barsa, J. A., 175
 Basmajian, J. V., 175
 Bauer, A. M., 189
 Bayne-Jones, S., 87
 Becattini, U., 175
 Beecher, H. K., 44, 46
 Behavior, 67
 associations of, 155
 base line method of analysis, 127-129
 biological basis of, 141
 causes of, 24
 comparative, 138-139

- development in children, 27
 stages of, 40-41
 disorders, 64
 drug therapy and, 69, 80, 145-146
 environmental changes influence, 67-68, 83, 117-118
 in free operant, 132-133
 investigation affects, 25-26
 measuring changes in, 69-73
 modification of, 39
 nonpatient studies in, 69
 pattern, 17
 psychodynamic approach to, 141
 psychological theories of, 71-72
 rating scales, 70-71
 relation to brain, 152-156, 159-161
 research, 22
 situation variables and, 65-67
 study of, 62-86
 probability of, 111, 112
 techniques for, 96-110
 theory of, 23, 36
 Belmont, E. H., 200
 Benactyzine (Suavitil), 11, 12, 13
 Benadryl, 39, 150. *See also* Diphenhydramine
 Benda, C. E., 68, 75, 175
 Bender, L., v, 35, 41, 42, 61, 85, 95, 160, 162, 175, 176, 186
 Bender-Gestalt test, 160
 Benzedrine, 39, 150. *See also* Amphetamine
 actions of, 39
 Bergman, P., 28, 33
 Berman, H. H., 176
 Bernard, C., 23, 25, 33
 Berry, R. V., 176
 Bijou, S. W., 44, 47, 102, 104, 124, 135
 Bills, R. R., 104
 Bleiberg, J., 176
 Block, S. L., 177
 Blood pressure, 6, 7
 Bobbitt, J. M., ix
 Body image, 56, 100
 Bonafede, V. I., 177
 Bonello, J. F., 177
 Borofsky, L. G., 174
 Borstelmann, L. J., v, 62-86, 109
 Boston, M., 33
 Bourne, H., 33
 Bouthilet, L., v, x, 170-206
 Bowen, M., 42, 177
 Bower, H. M., 177
 Bower, W. H., 177
 Bowlby, J., 33
 Bradley, C., 39, 42, 177, 178, 179
 Brady, J. V., 75
 Brain
 actions, reserpine and, 10
 injury, 153, 147
 schizophrenia and, 94
 visuomotor difficulties and, 160-161
 lesions, behavior and, 152-153
 relation to behavior, 152-156, 159-161
 structure, drugs affect, 52-53
 Braun, M., 179
 Bridge, E. M., 191
 Bromides, 4
 Buddy ratings, 101
 Buoniconto, P., 196
 Burgemeister, B. B., 201
 Butler, R. A., 135
 Caffeine, 15, 16
 Callahan, R. J., 104, 196
 Calmatives, nonbarbiturate, 4, 14
 Cantor, G. N., 68, 75
 Captodiamine (Suvren), 14
 Cardiac output, 5
 Cares, R. M., 179
 Carr, C. J., v, 3-20
 Carter, C. H., 179
 Castaneda, A., 104
 "Casualizing" drug, 12
 Cell assemblies, 166
 Cellular metabolism, 56
 Cerebral
 damage, 63
 functions, stimulation of, 17
 palsy, 63, 93
 stimulation, 16
 Charcowa, A. L., 172, 173
 Chess, S., 27, 33, 35
 Child guidance clinics, 77-78
 Child Welfare Research Station, 103

- Childhood, definition of, 37
 Children
 behavior
 disorders, 18-19
 study of, techniques for, 96-110
 "disturbed," xii, 3
 drugs and, vii
 effects in, xi, xii
 newer neuropharmacological, 48-61
 research in, basic issues, 21-47
 environmental effects on, 32-33
 operant conditioning techniques and, 111-136
 problems in studying, 144-147
 in Russia, study of, 169
 sociopathic, 31
 tranquilizers and, 49
 Chloral hydrate, 4
 Chlorpromazine (Thorazine), 5-6, 7, 8, 9, 39, 45, 92, 155, 164, 170
 Chow, K. L., 162
 Cleland, C., 171
 Cleveland, S. E., 104
 Cleveland, W. W., 180
 Clifford, S. H., v, 87-96
 Clothier, F., 180
 Cognition, development of, 67, 101-103
 Cole, J. O., v, ix, 3-20, 148
 Cole, K., v, 76, 109
 Compazine. *See* Prochlorperazine
 Convulsions, grand mal, 8
 Cooper, M., 34
 Cooperman, J. M., 191
 Cortex, inhibitory functions of, 10
 Cottington, F., 42, 175
 Craft, M., 180
 "Critical period hypothesis," 142
 Cromwell, R. L., 68, 75
 Cutler, M., 180
 Cutts, K. K., 180
 Cytryn, L., 34
 D-amphetamine (Dexedrine), 15, 16, 18, 164
 Dartal. *See* Thiopropazate
 Davidson, K., 105
 Davies, D. R., 167
 Deanol (Deaner), 15, 16, 19
 Deaner. *See* Deanol
 Deatrick, R. W., 196
 Delhagen, J. E., 135
 Dember, W. N., 135
 Denber, H. C. B., 181
 Denhoff, E., 181
 Dental procedure, tranquilizers and, 50
 Depression, 10, 12, 89
 affective, 5
 treatment of, 19
 Deprivation, 130, 131, 132
 Dermatitis, atopic, 50
 Deserpidine, 9
 Desoxyephedrine, 15, 16, 18
 Development
 physical, study of, 97-99
 problems of, 156-159
 social, 100-101
 variations in, 67
 Dexedrine, 80. *See also* D-amphetamine
 Di-isopropyl fluorophosphate, 164
 Dice, N., 181
 Dickson, W. J., 76
 Dihydroergotamine, 164
 Diphenhydramine (Benadryl), 4, 17
 Diphenylmethane derivatives, 4, 10-13, 50
 clinical use of, 13
 trade names of, 11
 Disipal. *See* Orphenadrine
 Doriden. *See* Glutethimide
 Dormison. *See* Methylparafynol
 Drake, M. E., 198
 Drive strength, 56
 Drives, 100
 Drugs
 action, biological and psychological
 mechanism of, vii
 clinical evaluation of, vii
 behavior analysis of, comparative, 137-151
 effect of, xi, xii
 in children, variables and, 144
 on development, 156-160
 misuse of, 168
 neuropharmacological, newer, 48-61
 major research needs in, 52-55

- clinical problems in, 54
 - constitutional problems in, 52-53
 - use in children's hospital, 50-52
 - peripheral actions of, 53
 - research
 - in children
 - basic issues of, 21-47
 - conceptual problems of, 21-26
 - special opportunities in, 26-31
 - ecological considerations in, 62-87
 - selection of subjects and behaviors in, 63
 - social implications of, 45
 - operant techniques in, 125-126
 - synthesis of, vii
 - tolerance, 156
- Dunnington, M. J., 104
- Durling, D., 181, 182
- EEG, 24
- Eayrs, J. T., 166, 167
- Eccles, A. K., 192
- Ectylurea (Nostyn), 14
- Effron, A. S., 42, 61, 182, 185
- Ehrmantraut, W. R., 183, 197
- Eiber, H. B., 182
- Eisenberg, L., v, 21-47, 102, 109, 141, 189
- Elam, C. B., 109
- Electroconvulsive therapy, 19
- Elkes, J. J., v, 163, 167
- Emotions
 - development of, 99-100
 - intelligence and, 29
 - reactions to, physiological tests of, 108
- Engel, G. L., 59, 61
- Enuresis, 50
- Enzyme systems, 166
- Epilepsy, 63
- Epinephrine, 15
- Equanil. *See* Meprobamate
- Equilibrium, adaptive or defensive, 59
- Escalona, S. K., 28, 33, 98
- Esen, F. M., 181, 182
- Ethchlorvynol (Placidyl), 14
- Ethinamate (Valmid), 14
- Ethyl alcohol, 4
- Experimental condition, 66
- Fabing, H. D., 182, 183
- Fabisch, W., 183
- Family relationship, behavior changes and, 59-60
- Fantasies, 79, 99
- Farrell, M. J., 68, 75
- Fazekas, J. F., 183, 197
- Fear, 12
- Felix, R. H., viii, 89
- Fenichel, M., 179
- Ferster, C. B., 115, 124, 135
- Finney, R. M., 194
- Fischer, E., 183
- Fischer, W., 76
- Fish, B., 95
- Fisher, S., v, x, xi, 97, 100, 104, 125, 132, 169, 170-206
- 5-hydroxytryptamine. *See* Serotonin
- Flach, F. F., 197
- Flaherty, J. A., 183
- Flemming, B. D., 109
- Forel, O. L., 109
- Frank, T., 188
- Freed, H., 45, 47, 76, 149, 151, 183, 184
- Freedman, A. M., vi, 28, 34, 42, 56, 58, 61, 95, 156, 182, 185
- Freedman, D. X., 162
- Frenquel. *See* Azacyclonol
- Freud, 36, 137
- Fuller, J. L., 142
- Galibert, 170
- Gallini, R., 175
- Garrison, M., Jr., 186
- Gastrointestinal tract, chlorpromazine and, 6
- Gatski, R. L., 186
- "General adjustment," 100
- Gerard, D. L., 186
- Gerard, R. W., 19, 147
- Gewirtz, J. L., vi, 124, 125, 127, 135
- Geyer, H. W., 186
- Ghent, L., vi, 152-167, 169
- Giedt, F. H., 76
- Gilbert, A., 34

- Gillette, H. E., 187
 Gillie, A. K., 186
 Ginn, S. A., 19, 187
 Giraud, 170
 Gladwin, T., 35, 105
 Glaser, K., 34
 Glutamic acid, 77
 Glutethimide (Doriden), 14
 Graham, B., 196
 Grayson, H. M., 76
 Green, E., 179
 Green, F., 42
 Greenberg, N. H., 34
 Greene, W. A., Jr., 59, 61
 Grossman, H. J., 34
 Gurevitz, S., 34

 Haber, J., 190
 "Habituation," 158-159
 Halkins, C. R., 191
 Hallucinations, 11
 Hallucinogens, 3-4
 Haq, S. M., 188
 Harlow, H. F., 135, 141, 142, 147
 Harlow, M. K., 135
 Harris, D. B., 147
 Harris, R. D., 188
 Hartson, L. D., 107, 109
 Hastings, M., 34
 Hawkins, J. R., 182, 183
 Hawthorne effect, 66
 Hebb, D. O., 158, 162
 Helme, W., 34, 42
 Helper, M. M., 104
 Henry, C. E., 190
 Hepatitis, 18
 Herold, W., 174
 Hess, E. H., 55
 Heuyer, 170
 Hexobarbital, 17
 Hinde, R. A., 132, 135
 Hofmann, 22
 Hohman, L. B., 19, 187
 Holden, R. H., 181
 Holland, J. G., 125
 Horenstein, S., 188
 Horowitz, L., 135
 Hospitalization, tranquilizers and, 60
 Hostility, 64

 House, B. J., 68, 76
 Howard, K. I., 104
 Hunt, A. D., 162
 Hunt, B. R., 188
 Hutt, P. J., 162
 Hydroxyzine (Atarax), 11, 12, 13
 Hyperactivity, 9, 64, 78, 107, 155
 Hyperkinesis, 92, 107
 in children, 31, 45, 50
 Hyperreflexia, 92
 Hypertension, 9
 Hypnotics, 3
 Hypotension, 7, 8, 9
 postural, 19

 Identity, 56
 Improvement, 31-32, 45-46, 69-73, 83
 Infants, autonomic reactivity in, 27
 Institute of Child Welfare, 140
 Intelligence, 28, 29
 development of, 98-99
 "sensorimotor," 29
 Iproniazid (Marsilid), 15, 17-18, 19,
 28
 actions of, 19
 Irwin, O. C., 109
 Isooctamethyl pyrophosphoramide, 164

 Jackson, B., 109
 Jasper, H. H., 180
 Jeri, R., 172
 Joseph, R., 188

 Kadji, L., 191
 Kamin, S. H., 176
 Kanner, L., 34, 189
 Kennard, M. A., 162
 Kidney, W., 189
 Killian, E., 171
 King, J. A., 147
 Kinnard, W. J., 19
 Kinross-Wright, V., 189, 194
 Kirk, D. L., 189
 Kish, G. B., 135
 Kline, A., 176
 Kline, N. S., 175, 189, 194
 Kling, J. W., 135
 Kohs Block Designs test, 160
 Koret, S., 56, 61

Krech, D., 167
 Kremer, M. W., 185
 Kritz, D., 186
 Krueger, D. E., 34
 Krush, T. P., 188
 Kubie, L. S., 56, 61
 Kugelmass, I. N., 189

Lambros, V. S., 190
 Landauer, W., 162
 Lanning, M., 198
 Lashley, K. S., 153, 161
 Laties, V. G., 14, 19
 Laufer, M. W., vi, 93
 Layman, E. M., vi, 50, 105, 133
 Lazar, M., 176
 Learning, 27, 28, 29, 37, 45, 67, 72,
 101

drug therapy and, 28-29, 149
 "to learn," 27, 141

measurement of, 102

process. *See also* Cognition

Benzedrine and, 39

Lehman, E., 190
 Lehtinen, L. E., 104
 Lemkau, P. V., 34
 Leon, C. A., 190
 Lepley, W. M., 127
 Leslie, G., 190
 Lesser, S. R., 190
 Levine, S., 143, 147
 Levy, S., 190
 Lewis, G. W., 147
 Lewis, L. F. E., 190
 Lezdins, V., 198
 Lighthall, F., 105
 Lindsley, D. B., 44, 190
 Lindsley, O. R., 46, 47, 124, 125
 Lipsitt, L. P., 104
 Lishman, W. A., 165
 Litchfield, H. R., 190
 Little, J. W., 180
 Liver
 drugs and, 18, 19
 function, 57
 Livingston, S., 191
 Long, E. R., vi, 44, 111-136, 169
 Lourie, R. S., vi, 48-61, 77, 83
 Low, N. L., 191

Lowery, V. E., 199
 Luhby, A., 191
 Lustman, S. L., 35
 Lysergic acid diethylamide (LSD), 11,
 13, 22, 156, 164

MacGillivray, R. C., 193
 MacGregor, J. M., 192
 Maley, M. C., 179
 Manic excitements, 8
 Marlowe, B., 34
 Marshall, H. R., 104
 Marsilid. *See* Iproniazid
 Marston, M. W., 147
 Masling, J. M., 101, 104
 Mathieson, C. M., 193
 Maturation, biological, 27
 Mautner, H., 181
 McCandless, B. R., vi, 71, 76, 96-110,
 133, 145

McCrory, W. W., 162

Mecham, M. J., 192

Mednick, S. A., 104

Meehl, P. E., 70, 76

Mental

defective, 63, 64, 68, 93

health, research in, vii

illness, drugs for, vii, 3

Mepazine (Pacatal), 5, 7, 8

Meprobamate (Equanil and Miltown),
 11, 13, 14

Meratran. *See* Pipradrol

Meredith, H. V., 97, 104

Merlis, S., 181

Mescaline, 13

Methamphetamine, 15, 16

Methylparafynol (Dormison), 14

Methylphenidate (Ritalin), 15, 16, 18

Methypylon (Noludar), 14

Meyer, A., 24

Meyer, D. R., 136

Miksztal, M. W., 192

Miles, R. C., 135

Mill, C. R., 79, 80, 81

Millen, F. J., 192

Miller, N., 138

Miltown. *See* Meprobamate

Miner, J. B., 109

Ming, C., 198

- Molitch, M., 192, 193
Monoamine oxidase inhibition, 10, 18
Morphine, 44
Morris, J. V., 193
Morton, H. G., 193
Moskowitz, H., 193
Motivation, 72, 97, 102, 118, 122, 123, 130
Motor development, 107
 study of, 97-98
Moulton, J. A. L., 183
Moyer, J. H., 194
Muscle
 skeletal, relaxation of, 13
 weakness, 7
Mussen, P. H., 105
Myers, G. G., 191

Narcotics, 3
Nathan, L. A., 194
National Institute of Mental Health, vii, ix, 62, 88, 89, 90, 91
National Institute of Neurological Diseases and Blindness, 88, 89
 project, 89, 90-92, 93
National Institutes of Health, xi, 87, 88
Nausea, 6, 8
Naylor, H. K., 105
Nellis, B., 171
Nervous system
 autonomic, chlorpromazine and, 6
 central, 11, 12, 24, 25
 cellular function, drugs and, 56
 intervention in functioning, 152-156
 stimulants, 45. *See also* Antidepressives
Neurons, 166
Neurophysiological problems, 152-167
Neuroses, drugs in, 3
Neurotics, 8, 11, 12, 13, 31, 89
Nichamin, S. J., 194
Nichtern, S., 42, 176, 194
Nicolaou, G. T., 194
Noe, O., 176
Noludar. *See* Methyprylon
Norepinephrine, 10
Norcross, K. J., 105
Nostyn. *See* Ectylurea

Nowlis, H. H., 58, 61
Nowlis, V., 58, 61

Obesity, drugs in, 16
Oettinger, L., Jr., 194, 195
Ogonik, J., 21
O'Neal, P., 26, 34
Operant conditioning techniques, use in children, 111-136
 free, 128-129
 responses, 111
Organismic sampling, 68-69
Orlando, R., 76
Ornitz, F. M., 162
Orphenadrine (Disipal), 4, 12, 15, 17, 19
Osmund, H., 42
O'Sullivan, C. J., 195
Oxanamide (Quiactin), 14

PRN. *see* Phenyltoloxamine
Pacatal. *See* Mepazine
Palermo, D. S., 104
Paregoric, 38
Parkinson's disease, 17
Parkinsonian side effects, 8, 10
Pasamanick, B., 34, 195
Pauli, L., 191
Pear, T. H., 109
Peifer, C. A., Jr., 184
Pennes, H. H., 19
Pentobarbital, 9, 16
Perception, 67, 72, 161
 drugs and, 56
Peripheral resistance, 5
Perkins, H. V., 105
Perlstein, M. A., 195
Perphenazine (Trilafon), 4, 7, 8, 9
Petrie, A., 109
Pharmacology, 3
Phenaglycodol (Ultran), 11, 13, 14
Phenergan. *See* Promethazine
Phenothiazine derivatives, 4, 5-9, 10, 22, 50
 clinical uses of, 8-9
 trade names of, 6
Phenyltoloxamine (PRN), 11, 12, 13
Phillips, R., 105
Physical development, study of, 97-99

- Piaget, J., 29, 30, 34, 35
 Picrotoxin, 164
 Pinneau, S. R., 35
 Pintler, M. H., 105
 Pipradrol (Meratran), 4, 11, 15, 16-17, 19
 Placebos, 66
 effects of, 44
 Placidyl. *See* Ethchlorvynol
 Pogge, R. C., 172
 Poliakoff, S., 193
 Pollack, M., 35
 Pomeranze, J., 196
 Populations, in child research, 62-86
 Prochlorperazine (Compazine), 5, 7, 8, 9
 Projective tests, 100, 135
 Promazine (Sparine), 6, 8
 Promethazine (Phenergan), 4
 Propanediol, 50
 Prouet, P. E., 196
 Prugh, D. G., vi, 55
 Psychiatry, child
 methodological problems in, 31-33
 needs in, 26
 "Psychic cost," 84-85
 Psychic stimulation, 15, 17
 Psychoactive drugs, review of, 3-20
 Psychological tests, drugs and, 80
 Psychology
 comparative, 137-140, 169
 development research in, 140, 144
 ego, 30
 Psychopathologist, 30
 Psychopharmacological agents, reference list on use of, 170-201
 Psychopharmacology
 comparative, 150, 151
 research in, vii, xi
 chance element, in, 22
 child, vii, ix, xi
 collaborative study in, 87-94
 objectives in, 92-93
 nonpatients, use of, 73-74, 80-81, 82-83
 scope of, 3-5
 Psychopharmacology Service Center, ix, x, xi, 62, 88, 89, 91, 92, 148, 171
 Psychosis
 childhood, 64
 manic phase of, 12
 Psychotics, 11
 apathetic, 9
 rating scales for, 89
 Psychotomimetics, 4
 Purcell, K., 105
 Pyridoxine, 158
 Quiactin. *See* Oxanamide
 Quinidine, 12
 RAS, 24
 Radke-Yarrow, M., 71, 76
 Rashkis, H. A., 76
 Rauwolfia alkaloids, 4, 9-10, 22, 50
 clinical use of, 10
 trade names of, 6
 Ray, P. K., 196
 Reading problems, 45
 drugs in children with, 16
 Redl, F., vi, 81
 Rees, E. L., 196
 Reflex patterns, 164
 Regression, hypothesis, 159-160, 166
 Reid, J. B., 109
 Reinforcement, 111, 114, 133, 134
 aversive, 124, 129
 conditioning, 131
 effect of, 121
 example of behavior in, 116-124
 intermittent, 114
 schedules of, 115-116
 Relaxants, 54
 Relearning, 108
 Reserpine, 9-10, 17, 154, 155
 actions of, 10
 Rescinnamine, 9
 Response typology, 27
 Responses, 114
 probability of, 116, 117
 rate of, 129
 Rettig, J. H., 196
 Richmond, J. B., 35
 Riskey, J. E., 167
 Ritalin. *See* Methylphenidate
 Robbins, L. N., 26, 34
 Robertiello, R. C., 185

- Robert, D. W., 34
 Robinson, M. E., 50
 Roethlisberger, F. J., 76
 Rorschach techniques, 99, 108
 Rosenblum, S., 196
 Rosenbluth, D., 33
 Rosenzweig, M. R., 165, 167
 Rosner, B. J., 162
 Rosner, S., 197
 Ross, S., vi, 137-151, 168, 169
 Rowley, E. H., 188
 Runge, G., 172
- Sack, P., 179
 Sainz, A., 197
 Sainz, A. A., 197
 Sarason, S. B., 35, 105
 Satiation, 118, 130, 131, 132
 Schiller, H., 176
 Schizophrenia, 8, 11, 13, 92, 108
 childhood, 94-95
 incidence of, 95
 origin of, 94
 chronic, 9
 drugs in, 3
 Scott, J. P., 147
 Scripture, E. W., 109
 Sears, R. R., 76, 99, 105
 Seashore, C. E., 109
 Sedation, 5, 9, 10, 14, 21, 96, 108
 Sedatives, nonbarbiturate, 4, 14
 clinical use of, 14
 trade names of, 14
 Segal, L. J., 76, 197
 Self concept, 56, 100
 Selling, L. S., 197
 Senn, M. J. E., vi, ix, 168-170
 Sensitivity, 27, 126
 Sensory
 cortex, stimulation of, 15
 deprivation, 108
 Serotonin (5-hydroxytryptamine), 9,
 10, 18
 Settel, E., 197
 Severino, J., 179
 Shannon, J. A., 87, 89
 Shea, J. G., 183, 197
 Sherwin, A. C., 197
 Sherrington, 163
- Silver, A. A., 39, 42, 198
 Situations, in child research, 62-86
 Skinner, B. F., 111, 112, 115, 124,
 125, 127, 135, 136
 Sleep problems, 50
 Smarr, E. R., 76
 Smith, G. F., 180
 Smith, W. I., 147
 Smyth, V. O. G., 188
 Social development, 100-101
 Soderberg, C., 192
 Souder, C. L. R., 197
 Sparine. *See* Promazine
 Sparup, K. H., 198
 Spatial orientation, 160-161
 Spiegel, E. A., 174
 Spiegel, J., 59, 61
 Spiker, C. C., 76, 101, 105
 Sprogis, G. R., 198
 Stability, 27, 28, 126
 Stabilimeter, 107
 Stanley, A. M., 189
 Staudt, V. M., 35
 Steigman, A. J., 198, 199
 Stelazine. *See* Trifluoperazine
 Stetson, R. H., 107, 110
 Stevenson, H. W., 68, 76
 Stimulants, 4, 14-19, 45, 54
 Stimulus generalization, 103
 Stokes, J., 161
 Stokes, P. E., 197
 Strauss, A. A., 180
 Stritzler, C., 199
 Stromsta, C., 192
 Stroud, H. H., 162
 Suavitil. *See* Benactyzine
 Substituted diols, 4, 13-14
 clinical use of, 13-14
 trade name, 11
 Sullivan, J. P., 193
 Sullivan, P. D., Jr., 197
 Surgical procedures, tranquilizers and,
 50
 Suvren. *See* Captodiamine
 Symptoms
 masking of, 53-54
 substitution of, 59
 Szatmari, A., 175
 Szekely, E. G., 174

- Tachycardia, 5
Talbot, M. W., Jr., 199
Tansley, A. E., 76, 197
Tarjan, G., 199
Teicher, J. D., 199
Tension, 11, 14
Thiopropazate (Dartal), 7, 8
Thomas, A., 27, 33, 35
Thorazine, 79. *See also* Chlopromazine
Ticktin, H. E., 197
Timberlake, W. H., 200
Tinbergen, N., 147
Todrick, A., 167
Tolman, R. S., 76
Toxic or side effects, 9, 10, 19, 55, 57
Tranquilization, 5
 psychic costs of, 28
Tranquilizers, 39, 77, 150
 constitutional problems and, 52-53
 dangers of, 55
 development of, 48-49, 60-61
 evaluation of effects in children, 58
 major, 4
 phenothiazine derivatives, 4, 5-9
 rauwolfia alkaloids, 4
 minor, 4, 10
 diplenylnmethane derivatives, 4
 substituted diols, 4
 problems of development and, 54-55
 psychophysiological and behavioral
 studies and, 56
 toxic and side effects in children, 57
 use
 in children's hospital, 50
 in Russia, 169
 variables influencing effects of, 57-58
Tricresylphosphate, 164
Trifluoperazine (Stelazine), 5, 8, 9
Triflupromazine (Vesprin), 7, 8
Trilafon, 7
Trouton, D. S., 76
Truitt, E. B., Jr., 20
Tsang, Y. C., 163
Tyler, D. W., 109
Ultran. *See* Phenaglycodol
Vallbona, C., 199
Valmid. *See* Ethinamate
Vergani, O., 200
Verplanck, W. S., 125, 131, 136
Vesprin. *See* Triflupromazine
Villa, A. P., 172, 173
"Voluntary responses," 111
Vomiting, 50
Waelsch, H., 167
Waggoner, R. W., 181
Waite, R., 105
Walsh, A. M., 104, 105
Warson, S. R., 193
Watkins, C., 200
Weir, H. F., 200
Weiss, B., 14, 19
Weisselberger, D., 186
Wenzel, B., 154, 163
White, S. D., 198
Wikler, A., 20, 61
Williams, R. J., 76
Winkelman, N. W., Jr., 201
Wittenborn, J. R., 70, 76
Wolfson, I. N., 201
Wright, S. W., 199
Wycis, H. T., 174
Wyckoff, G., 198
Yarrow, J. J., 76
Yerkes, R., 139
Zeaman, D., 76
Zigler, E. F., 68, 76
Zimmerman, F. T., 201
Zubin, J., 35
Zwilling, E., 163

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